R

Journal of The Chemical Society

DETROIT PUBLIC LIBRARY
DEC 2 9 1959
TECHNOLOGY DEPARTMENT

November 1959

XUM

PUBLICATION COMMITTEE

Chairman

H. J. Emeléus, C.B.E., M.A., D.Sc., F.R.S.

C. C. Addison, D.Sc., Ph.D., F.R.I.C.
Wilson Baker, M.A., D.Sc., F.R.S.
E. Boyland, D.Sc., Ph.D.
I. G. M. Campbell, B.Sc., Ph.D.
N. Campbell, D.Sc., Ph.D.
N. B. Chapman, M.A., Ph.D.
J. Chatt, M.A., Sc.D., F.R.I.C.
P. B. D. de la Mare, D.Sc., Ph.D.
D. D. Eley, Sc.D., Ph.D.
D. H. Everett, M.B.E., M.A., D.Phil.
G. Gee, Sc.D., A.R.I.C., F.R.S.
R. H. Hall, Ph.D., A.R.C.S., F.R.I.C.
T. G. Halsall, Ph.D., M.A., A.R.I.C.
D. H. Hey, D.Sc., F.R.I.C., F.R.S.
D. J. G. Ives, D.Sc., A.R.C.S., F.R.I.C.
A. W. Johnson, Sc.D., Ph.D., A.R.C.S.
C. Kemball, M.A., Ph.D., F.R.I.C.
G. W. Kenner, M.Sc., Ph.D.
J. A. Kitchener, D.Sc., Ph.D.
H. C. Longuet-Higgins, M.A., D.Phil., F.R.S.
B. Lythgoe, M.A., Ph.D., F.R.I.C., F.R.S.
A. Neuberger, Ph.D., M.D., F.R.S.
H. T. Openshaw, M.A., D.Phil.
M. W. Perrin, C.B.E., M.A., F.R.I.C.
V. Petrow, Ph.D., D.Sc., F.R.I.C.
R. A. Raphael, D.Sc., A.R.C.S., F.R.I.C.
P. L. Robinson, D.Sc., F.R.I.C.
K. Schofield, Ph.D., D.Sc., F.R.I.C.
A. G. Sharpe, M.A., Ph.D., F.R.I.C.
J. C. Speakman, M.Sc., Ph.D., D.Sc.
K. W. Sykes, M.A., D.Phil.
A. R. J. P. Ubbelohde, M.A., D.Sc., F.R.S.
B. C. L. Weedon, D.Sc., A.R.C.S., F.R.I.C.
D. H. Whiffen, M.A., D.Phil.

Editor

R. S. Cahn, M.A., D.Phil.Nat., F.R.I.C.

Deputy Editor

L. C. Cross, Ph.D., A.R.C.S., F.R.I.C.

Assistant Editors

A. D. Mitchell, D.Sc., F.R.I.C.
J. B. Poole, B.A.

Subscription rate to non-Fellows £20 0*s.* 0*d.* (including Proceedings) per annum post free.

CHEM. SOC., 1941–1944—REPRINT

The Journal of The Chemical Society for the four years 1941–1944 has now been reprinted and is available, price £10 per year, from the Society. Orders for these volumes, and enquiries for other back-issues, are invited.

THE CHEMICAL SOCIETY,
BURLINGTON HOUSE, LONDON, W.1.

XUM

XUM

CONTENTS

General, physical, and inorganic

NO.		PAGE
634	Metallic salts as promoters in hydrogenation with platinum oxide catalysts By E. B. MAXTED and SAYEED AKHTAR	3130
642	Peroxides of elements other than carbon. Part V. The formation of cadmium peroxides by autoxidation and by nucleophilic substitution By ALWYN G. DAVIES and J. E. PACKER	3164
646	Norbornadiene–metal complexes and some related compounds By E. W. ABEL, M. A. BENNETT, and G. WILKINSON	3178
654	Kinetics of the bromination of acetone in concentrated aqueous hydrochloric acid By G. ARCHER and R. P. BELL	3228
658	The π-electronic structure and properties of naphthalene By T. E. PEACOCK	3241
659	The crystallography of some cyanine dyes By P. J. WHEATLEY	3245
664	Structure and reactivity of the oxyanions of transition metals. Part VI. Photolysis of chromate, permanganate, and related compounds in rigid media at low temperatures By U. KLÄNING and M. C. R. SYMONS	3269
669	The thermal decomposition of cæsium permanganate By P. J. HERLEY and E. G. PROUT	3300
671	Exchange studies of certain chelate compounds of the transitional metals. Part VII. Substituent effects on the dissociation rates of nickel(II)–phenanthroline and –bipyridyl complexes By PETER ELLIS, R. HOGG (in part), and R. G. WILKINS	3308
677	The interpretation of the energies of activation of some reactions of aromatic nitro-compounds By E. F. CALDIN	3345
686	The barium fluoride–uranium tetrafluoride and the strontium fluoride–thorium tetrafluoride system By R. W. M. D'EYE and I. F. FERGUSON	3401
687	Organosilyloxy-derivatives of metals. Part I. Alkylsilyloxy-derivatives of titanium, zirconium, niobium, and tantalum By D. C. BRADLEY and I. M. THOMAS	3404
694	The infrared spectra of some compounds containing the trifluoromethylthio-group, $CF_3 \cdot S \cdot$ By S. N. NABI and N. SHEPPARD	3439
695	Distribution of molecular weights in some polyesters and polypeptides By M. T. POPE, T. J. WEAKLEY, and R. J. P. WILLIAMS	3442
696	The spectrum of the coronene crystal By L. E. LYONS and J. R. WALSH	3447
699	Mechanism of the azide–nitrite reaction. Part III. Reaction in [^{18}O]water By C. A. BUNTON and G. STEDMAN	3466
700	Comparison of some properties of anhydrous sulphuric acid and dideuterosulphuric acid over a range of temperature By N. N. GREENWOOD and A. THOMPSON	3474
701	The mechanism of electrical conduction in fused phosphoric and trideuterophosphoric acids By N. N. GREENWOOD and A. THOMPSON	3485
702	Addition compounds of boron trifluoride with orthophosphoric and trideuterophosphoric acids By N. N. GREENWOOD and A. THOMPSON	3493

XUM

NO. PAGE

713 The stretching frequencies of metal–oxygen double bonds
By C. G. BARRACLOUGH, J. LEWIS, and R. S. NYHOLM 3552

715 The catalytic hydrogenation of unsaturated hydrocarbons. Part IV. The kinetics of the hydrogenation of acetylene over supported and unsupported iron, cobalt, and copper, and over some nickel–cobalt and nickel–copper alloys
By G. C. BOND and R. S. MANN 3566

718 The kinetics of formation of some polyesters
By M. T. POPE and R. J. P. WILLIAMS 3579

NOTES

728 Reactions of disodium pentacyanoamminoferrate with aromatic amines. Part IV. The preparation and properties of compounds containing the μ-*p*-phenylenediamine-bis(pentacyanoferrate) ion
By E. F. G. HERINGTON 3633

732 *p*-Bisphenylmercuribenzene
By M. MALNAR and D. GRDENIĆ 3639

736 The reactions of boron halides with anhydrous sulphuric acid: boron tri(hydrogen sulphate) and tetra(hydrogen sulphato)boric acid
By N. N. GREENWOOD and A. THOMPSON 3643

744 Measurement of the conductance of electrolytes
By W. S. METCALF 3654

Physical organic

630 The rates of reaction of αα-diphenyl-β-picrylhydrazyl with certain amines and phenols
By J. C. MCGOWAN, T. POWELL, and R. RAW 3103

632 Nitrosation, diazotisation, and deamination. Part VII. The reactivities of some aromatic amines towards dinitrogen trioxide
By L. F. LARKWORTHY 3116

635 Aromatic alkylation. Part III. Comparison of the reactivities of some aromatic compounds towards diphenylcarbonium ions
By D. BETHEL, V. GOLD, and T. RILEY 3134

641 Tautomerism and geometrical isomerism of arylazo-phenols and -naphthols. Part I. 4-Phenylazo-1-naphthol
By ERNST FISCHER and (MRS.) YAEL F. FREI 3159

644 The effect of viscosity on the fluorescence yield of solutions
By E. J. BOWEN and S. F. A. MISKIN 3172

655 The decomposition of nitramide in *m*-cresol catalysed by aniline derivatives
By W. W. CARNIE, P. M. DUNCAN, J. A. KERR, KATHLEEN SHANNON, A. F. TROTMAN-DICKENSON, and J. A. WHITE 3231

662 Autoxidation. Part I. Liquid-phase autoxidation of 5-methylnonane
By R. R. ARNDT, J. B. BARBOUR (in part), (MISS) E. J. ENGELS, D. H. S. HORN, and D. A. SUTTON 3258

665 Ultraviolet and infrared spectra of some aromatic nitro-compounds
By C. P. CONDUIT 3273

670 Nitrosation, diazotisation, and deamination. Part VIII. The diazotisation of weakly basic amines in dilute perchloric acid
By L. F. LARKWORTHY 3304

693 Physicochemical studies on starches. Part XX. The existence of an anomalous amylopectin in starch
By W. BANKS and C. T. GREENWOOD 3436

697 A theoretical treatment of the chemistry of quinoline
By R. D. BROWN and R. D. HARCOURT 3451

703 Vapour-phase photochemical chlorination and bromination of 2,2,4,4-tetramethylpentane
By J. D. BACKHURST 3497

NO. PAGE

704 Infrared absorption of heteroaromatic, five-membered, monocyclic nuclei. Part II. 2-Monosubstituted thiophens
By A. R. KATRITZKY and A. J. BOULTON 3500

706 The reaction of 1,3,5-trinitrobenzene with aliphatic amines
By R. FOSTER 3508

708 Physical properties and chemical constitution. Part XXVII. Dipole moments of some cyclic ethers, sulphides, sulphoxides, and sulphones
By C. W. N. CUMPER and A. I. VOGEL 3521

716 Substituent effects in fluorene derivatives. Part I. The reaction of substituted 9-bromofluorenes with potassium iodide in acetone
By J. D. DICKINSON and C. EABORN 3574

719 The conductance of solutions in which the solvent molecule is " large." Part IV. Amine picrates in triethyl phosphate
By C. M. FRENCH, P. B. HART, and D. F. MUGGLETON 3582

NOTES

733 Aromatic reactivity. Part VII. Additivity of effects of methyl substituents in protodesilylation
By C. EABORN and R. C. MOORE 3640

734 Substituent effects in fluorene compounds. Part II. Substituted 9-fluorenones in oxime formation
By J. D. DICKINSON and C. EABORN 3641

737 A molecular orbital calculation of the ultraviolet absorption spectrum of the quinolizinium cation
By T. E. PEACOCK 3645

739 The stability constants of some metal chelates of *ortho*aminophenols
By PETER SIMS 3648

Organic

631 Azatropolones
By A. H. REES 3111

633 The substitution of azulene by benzyl radicals
By J. F. TILNEY-BASSETT and WILLIAM A. WATERS 3123

636 The tropylium ion. Part V. Synthesis of cyclopropa[*l*]phenanthrene derivatives and attempted formation of the dibenzo[*a*,*c*]tropylium cation
By M. J. S. DEWAR and C. R. GANELLIN 3139

637 1,2:3,4:5,6:7,8:9,10:11,12-Hexabenzotriphenylene
By JOHN G. CAREY and IAN T. MILLAR 3144

638 Studies in relation to biosynthesis. Part XX. The structure and biosynthesis of curvularin
By A. J. BIRCH, O. C. MUSGRAVE, R. W. RICKARDS, and HERCHEL SMITH . . 3146

639 Degradative studies of peptides and proteins. Part V. The formation of 2-acylimino-3-methylthiazolid-5-ones from *N*-acylthiocarbamoylsarcosine derivatives and their behaviour towards nucleophilic reagents
By D. T. ELMORE 3152

640 Formation of 2′-hydroxyimidazo(4′,5′:2,3)pyridine from the hydrazides and hydroxamic acids of 2-aminonicotinic and 3-aminopicolinic acids
By D. HARRISON and A. C. B. SMITH 3157

643 Mechanism of hydrogenation. Part II. Acid catalysis of hydrogenolysis of epoxides and of allyl alcohol derivatives
By F. J. MCQUILLIN and W. O. ORD 3169

645 Liquid-phase photolysis. Part I. Variation of isomer ratios with radical source in the phenylation of isopropylbenzene. Photolytic generation of phenyl radicals
By J. MCDONALD BLAIR, D. BRYCE-SMITH, and B. W. PENGILLY 3174

647 The relative stabilising influences of substituents on free alkyl radicals. Part VI. The cleavage of substituted dibenzyl ethers by Grignard reagents in the presence of cobaltous chloride
By R. L. HUANG and SURINDER SINGH 3183

XUM

NO.		PAGE
648	The relative stabilising influences of substituents on free alkyl radicals. Part VII. The cleavage of monosubstituted dibenzyl ethers by free t-butoxy-radicals By R. L. Huang and Oon-Keong Yeo	3190
649	The steroid series. Part IV. Some basic derivatives By A. F. Chaplin, D. H. Hey, and J. Honeyman	3194
650	Diazaindenes and their quaternary salts. Part I. The preparation of 2,3,3-trimethyl-3*H*-1,7-diazaindene, and its methiodides and derived cyanine dyes By G. E. Ficken and J. D. Kendall	3202
651	The reaction of phenyl- and 2,4-dinitrophenyl-hydrazine with some unsaturated glucose derivatives By W. M. Corbett	3213
652	The oxidation of derivatives of *o*-phenylenediamine. Part VII. Bromination of anilinoaposafranines and related compounds By Vincent C. Barry, J. G. Belton, J. F. O'Sullivan, and Dermot Twomey	3217
653	The structure of Floridean starch. Part I. Linkage analysis by partial acid hydrolysis By Stanley Peat, J. R. Turvey, and J. M. Evans	3223
656	Thiophen derivatives. Part XIV. Some problems of substitution in the 2,2′-bithienyl series By E. Lescot, jun., Ng. Ph. Buu-Hoï, and N. D. Xuong	3234
657	Cyclodehydration of arylidene-α-tetralones derived from fluorene, dibenzofuran, and dibenzothiophen By G. Saint-Ruf, Ng. Ph. Buu-Hoï, and P. Jacquignon	3237
660	Muscarufin. Part I. The action of diazotised anthranilic acid on 1,4-benzoquinones By R. L. Edwards and D. G. Lewis	3250
661	Muscarufin. Part II. 2-(4-carboxybuta-1,3-dienyl)-1,4-benzoquinones By R. L. Edwards and D. G. Lewis	3254
663	Studies of *Aspergillus niger*. Part XI. Enzymic synthesis of a pseudoaldobiuronic acid By S. A. Barker, A. Gómez-Sánchez, and M. Stacey	3264
666	Organic fluorine compounds. Part XI. Ethyl fluoroacetoacetates and fluoropyrimidines By Ernst D. Bergmann, S. Cohen, and I. Shahak	3278
667	Organic fluorine compounds. Part XII. Preparation and reactions of diethyl fluoromalonate By Ernst D. Bergmann, Sasson Cohen, and Israel Shahak	3286
668	The chemistry of the *Aristolochia* species. Part IV. The structure of aristolactone By J. W. Steele, J. B. Stenlake, and W. D. Williams	3289
672	Reaction of periodate with compounds containing active methylene groups By J. L. Bose, A. B. Foster, and R. W. Stephens	3314
673	The constitution and stereochemistry of drimenol, a novel bicyclic sesquiterpenoid By H. H. Appel, C. J. W. Brooks, and K. H. Overton	3322
674	Naphthimidazoles. Part II. 5,6,7,8-Tetrahydronaphth[2,3]imidazole and some derivatives By D. J. Brown and R. J. Harrisson	3332
675	Lactones. Part VI. The preparation of 5,7-dihydroxyphthalide, its 5-methyl ether, and related compounds By W. R. Allison and G. T. Newbold	3335
676	The structure of Floridean starch. Part II. Enzymic hydrolysis and other studies By Stanley Peat, J. R. Turvey, and J. M. Evans	3341
678	Tocopherols. Part III. Reaction of phytol with some toluquinol derivatives By P. Mamalis, J. Green, S. Marcinkiewicz, and D. McHale	3350
679	Tocopherols. Part IV. Synthesis of 5-methyltocol By D. McHale, P. Mamalis, S. Marcinkiewicz, and J. Green	3358

NO.		PAGE
680	Tocopherols. Part V. Structural studies on ε- and ζ-tocopherol By J. GREEN, D. MCHALE, S. MARCINKIEWICZ, P. MAMALIS, and P. R. WATT	3362
681	Tocopherols. Part VI. A novel synthesis of 8-methyltocol By J. GREEN, D. MCHALE, P. MAMALIS, and S. MARCINKIEWICZ	3374
682	Tocopherols. Part VII. The condensation of toluquinol with phytol By S. MARCINKIEWICZ, D. MCHALE, P. MAMALIS, and J. GREEN	3377
683	Diaryls. Part II. The rearrangement of 1,2′-hydrazonaphthalene By E. R. WARD and B. D. PEARSON	3378
684	Steric effects in 2,2′-bridged diphenyls with a heterocyclic bridging ring. Part II. An optically active tetrahydrodibenzazocine By SHAKTI R. AHMED and D. MURIEL HALL	3383
685	The synthesis of some indolylalkylamines By (MRS.) A. F. AMES, D. E. AMES, C. R. COYNE, T. F. GREY, I. M. LOCKHART, and R. S. RALPH	3388
688	Hydropteridines. Part V. 7,8-Dihydro-6-hydroxypteridine-4-carboxylic acids By JIM CLARK and A. J. LAYTON	3411
689	Colouring matters derived from pyrroles. Part II. Improved syntheses of some dipyrromethenes and porphyrins By A. W. JOHNSON, I. T. KAY, E. MARKHAM, R. PRICE, and K. B. SHAW	3416
690	Coloured alkali salts from *sym.*-trinitrobenzene derivatives. Part I. Picryl derivatives By R. C. FARMER	3425
691	Coloured alkali salts from *sym.*-trinitrobenzene derivatives. Part II. Phenoxy-compounds By R. C. FARMER	3430
692	Coloured alkali salts from *sym.*-trinitrobenzene derivatives. Part III. Picramide derivatives By R. C. FARMER	3433
698	The stereochemistry of the tropane alkaloids. Part XII. The total synthesis of scopolamine By P. DOBÓ, G. FODOR, G. JANZSÓ, I. KOCZOR, J. TÓTH, and I. VINCZE	3461
705	Phenacyl sulphides and related compounds. Part I. The action of alkali on *o*-nitrophenyl phenacyl sulphide By K. J. MORGAN	3502
707	Ipecacuanha alkaloids. Part IV. The relative and absolute stereochemistry of the benzoquinolizidine system of emetine By A. R. BATTERSBY and S. GARRATT (née COX)	3512
709	Methylperylenes. Part I. Synthesis of 1-, 2-, and 3-methylperylene By A. D. CAMPBELL, R. A. ELDER, and G. W. EMERSON	3526
710	Chemical constitution and amœbicidal action. Part IV. Synthesis of emetine and stereoisomers of emetine By M. BARASH, J. M. OSBOND, and J. C. WICKENS	3530
711	Cyclodehydration processes. Part II. Migration of a phenyl group during cyclisation of ω-phenoxyacetophenone By W. DAVIES and S. MIDDLETON	3544
712	Phospholipids. Part V. The hydrolysis of the glycerol 1-esters of myoinositol 1- and 2-phosphate By D. M. BROWN, G. E. HALL, and R. LETTERS	3547
714	The preparation and reactions of some optically active substituted benzhydrols By R. T. PUCKOWSKI and W. A. ROSS	3555
717	Submicro-methods for the analysis of organic compounds. Part X. Determination of fluorine By R. BELCHER, M. A. LEONARD, and T. S. WEST	3577
720	Tropolones. Part X. Synthesis and properties of 2,3-benzotropone By G. L. BUCHANAN and D. R. LOCKHART	3586
721	Modified steroid hormones. Part XI. 15α-Methyldeoxycorticosterone acetate By VLADIMIR PETROW and DAVID M. WILLIAMSON	3595

NO. PAGE

722 The chemistry of fungi. Part XXXVII. The structure of rubropunctatin
By E. J. Haws, J. S. E. Holker, A. Kelly, A. D. G. Powell, and Alexander Robertson 3598

723 Bis-*o*-phenylene pyrophosphite: a new reagent for peptide synthesis. Part II. Some peptide syntheses with the new reagent
By P. C. Crofts, J. H. H. Markes, and H. N. Rydon 3610

724 Some *NN*-Di-2-chloroalkyl derivatives of carboxyamides and sulphonamides
By W. C. J. Ross and J. G. Wilson 3616

725 The oxygen groups of cassaic acid
By V. P. Arya and David W. Mathieson 3623

726 The hydrolysis of D-carboxyethylene phosphate (D-glyceric acid 2,3-cyclic phosphate)
By R. F. Webb and A. J. Duke 3627

727 Chemical constitution and amœbicidal action. Part V. Stereochemistry of emetine
By A. Brossi, A. Cohen, J. M. Osbond, P. Plattner, O. Schnider, and J. C. Wickens 3630

Notes

729 Preparation of 1-benzylpiperazine
By J. Cymerman Craig 3634

730 Isomer ratios in the nitration of 6-acylamino-1,2,3,4-tetrahydronaphthalenes
By E. R. Ward and B. D. Pearson 3635

731 The periodate oxidation of 2-deoxyglycosides: structure of 1-(2-deoxy-D-galactosyl)benzimidazole
By R. J. Ferrier and W. G. Overend 3638

735 Synthesis of α-azido-γ-butyrolactone and its reduction to α-amino-compounds
By Max Frankel, Y. Knobler, and T. Sheradsky 3642

738 Pyrimidine reactions. Part II. 2-Ethoxy-4-, and 4-ethoxy-2-hydroxy-5-nitropyrimidine
By D. J. Brown 3647

740 2,3:6,7-Dibenzodiphenylene
By R. F. Curtis 3650

741 6-Hydroxy-4,5-benzindane
By David W. Mathieson and V. S. Gandhi 3650

742 Experiments relating to phthiocerol. Part IV. Synthesis of 7-methoxy-6-methylnonanoic acid
By F. K. Drayson and N. Polgar 3652

743 Polyfluoroarenes. Part II. The ionisation constant of pentafluorophenol
By J. M. Birchall and R. N. Haszeldine 3653

INDEX OF AUTHORS' NAMES

ABEL, E. W., Bennett, M. A., and Wilkinson, G., 3178
Ahmed, S. R., and Hall, D. M., 3383
Akhtar, S. See Maxted, E. B., 3130
Allison, W. R., and Newbold, G. T., 3335
Ames, A. F., Ames, D. E., Coyne, C. R., Grey, T. F., Lockhart, I. M., and Ralph, R. S., 3388
Ames, D. E. See Ames, A. F., 3388
Appel, H. H., Brooks, C. J. W., and Overton, K. H., 3322
Archer, G., and Bell, R. P., 3228
Arndt, R. R., Barbour, J. B., Engels, E. J., Horn, D. H. S., and Sutton, D. A., 3258
Arya, V. P., and Mathieson, D. W., 3623
Backhurst, J. D., 3497
Banks, W., Greenwood, C. T., 3436
Barash, M., Osbond, J. M., and Wickens, J. C., 3530
Barbour, J. B. See Arndt, R. R., 3258
Barker, S. A., Gómez-Sánchez, A., and Stacey, M., 3264
Barraclough, C. G., Lewis, J., and Nyholm, R. S., 3552
Barry, V. C., Belton, J. G., O'Sullivan, J. F., and Twomey, D., 3217
Battersby, A. R., and Garratt, S., 3512
Belcher, R., Leonard, M. A., and West, T. S., 3577
Bell, R. P. See Archer, G., 3228
Belton, J. G. See Barry, V. C., 3217
Bennett, M. A. See Abel, E. W., 3178
Bergmann, E. D., Cohen, S., and Shahak, I., 3278, 3286
Bethel, D., Gold, V., and Riley, T., 3134
Birch, A. J., Musgrave, O. C., Rickards, R. W., and Smith, H., 3146
Birchall, J. M., and Haszeldine, R. N., 3653
Blair, J. M., Bryce-Smith, D., and Pengilly, B. W., 3174
Bond, G. C., and Mann, R. S., 3566
Bose, J. L., Foster, A. B., and Stephens, R. W., 3314
Boulton, A. J. See Katritzky, A. R., 3500
Bowen, E. J., and Miskin, S. F. A., 3172
Bradley, D. C., and Thomas, I. M., 3404
Brooks, C. J. W. See Appel, H. H., 3322
Brossi, A., Cohen, A., Osbond, J. M., Plattner, P., Schnider, O., and Wickens, J. C., 3630
Brown, D. J., 3647
Brown, D. J., and Harrisson, R. J., 3332
Brown, D. M., Hall, G. E., and Letters, R., 3547
Brown, R. D., and Harcourt, R. D., 3451
Bryce-Smith, D. See Blair, J. M., 3174
Buchanan, G. L., and Lockhart, D. R., 3586
Bunton, C. A., and Stedman, G., 3466
Buu-Hoï, Ng. Ph. See Lescot, E., jun., 3234, and Saint-Ruf, G., 3237
Caldin, E. F., 3345
Campbell, A. D., Elder, R. A., and Emerson, G. W., 3526
Carey, J. G., and Millar, I. T., 3144
Carnie, W. W., Duncan, P. M., Kerr, J. A., Shannon, K., Trotman-Dickenson, A. F., and White, J. A., 3231
Chaplin, A. F., Hey, D. H., and Honeyman, J., 3194
Clark, J., and Layton, A. J., 3411
Cohen, A. See Brossi, A., 3630
Cohen, S. See Bergmann, E. D., 3278, 3286
Conduit, C. P., 3273
Corbett, W. M., 3213
Coyne, C. R. See Ames, A. F., 3388
Crofts, P. C., Markes, J. H. H., and Rydon, H. N., 3610
Cumper, C. W. N., and Vogel, A. I., 3521
Curtis, R. F., 3650
Cymerman Craig, J., 3634
Davies, A. G., and Packer, J. E., 3164
Davies, W., and Middleton, S., 3544
Dewar, M. J. S., and Ganellin, C. R., 3139
D'Eye, R. W. M., and Ferguson, I. F., 3401
Dickinson, J. D., and Eaborn, C., 3574, 3641
Dobó, P., Fodor, G., Janzsó, G., Koczor, I., Tóth, J., and Vincze, I., 3461
Drayson, F. K., and Polgar, N., 3652
Duke, A. J. See Webb, R. F., 3627
Duncan, P. M. See Carnie, W. W., 3231
Eaborn, C., and Moore, R. C., 3640
Eaborn, C. See also Dickinson, J. D., 3574, 3641
Edwards, R. L., and Lewis, D. G., 3250, 3254
Elder, R. A. See Campbell, A. D., 3526
Ellis, P., Hogg, R., and Wilkins, R. G., 3308
Elmore, D. T., 3152
Emerson, G. W. See Campbell, A. D., 3526
Engels, E. J. See Arndt, R. R., 3258
Evans, J. M. See Peat, S., 3223, 3341
Farmer, R. C., 3425, 3430, 3433
Ferguson, I. F. See D'Eye, R. W. M., 3401
Ferrier, R. J., and Overend, W. G., 3638
Ficken, G. E., and Kendall, J. D., 3202
Fischer, E., and Frei, Y. F., 3159
Fodor, G. See Dobó, P., 3461
Foster, A. B. See Bose, J. L., 3314
Foster, R., 3508
Frankel, M., Knobler, Y., and Sheradsky, T., 3642
Frei, Y. F. See Fischer, E., 3159
French, C. M., Hart, P. B., and Muggleton, D. F., 3582
Gandhi, V. S. See Mathieson, D. W., 3650
Ganellin, C. R. See Dewar, M. J. S., 3139
Garratt, S. See Battersby, A. R., 3512
Gómez-Sánchez, A. See Barker, S. A., 3264
Green, J., McHale, D., Mamalis, P., and Mancinkiewicz, S., 3374
Green, J., McHale, D., Marcinkiewicz, S., Mamalis, P., and Watt, P. R., 3362
Green, J. See also McHale, D., 3358, Mamalis, P., 3350, and Marcinkiewicz, S., 3377
Greenwood, C. T. See Banks, W., 3436
Greenwood, N. N., and Thompson, A., 3474, 3485, 3493, 3643
Gold, V. See Bethel, D., 3134
Grdenić, D. See Malnar, M., 3639
Grey, T. F. See Ames, A. F., 3388
Hall, G. E. See Brown, D. M., 3547
Hall, D. M. See Ahmed, S. R., 3383
Harcourt, R. D. See Brown, R. D., 3451
Harrison, D., and Smith, A. C. B., 3157
Harrisson, R. J. See Brown, D. J., 3332
Hart, P. B. See French, C. M., 3582
Haszeldine, R. N. See Birchall, J. M., 3653
Haws, E. J., Holker, J. S. E., Kelly, A., Powell, A. D. G., and Robertson, A., 3598
Herington, E. F. G., 3633
Herley, P. J., and Prout, E. G., 3300

Hey, D. H. See Chaplin, A. F., 3194
Hogg, R. See Ellis, P., 3308
Holker, J. S. E. See Haws, E. J., 3598
Honeyman, J. See Chaplin, A. F., 3194
Horn, D. H. S. See Arndt, R. R., 3258
Huang, R. L., and Singh, S., 3183
Huang, R. L., and Yeo, O-K., 3190
Jacquignon, P. See Saint-Ruf, G., 3237
Janzsó, G. See Dobó, P., 3461
Johnson, A. W., Kay, I. T., Markham, E., Price, R., and Shaw, K. B., 3416
Katritzky, A. R., and Boulton, A. J., 3500
Kay, I. T. See Johnson, A. W., 3416
Kelly, A. See Haws, E. J., 3598
Kendall, J. D. See Ficken, G. E., 3202
Kerr, J. A. See Carnie, W. W., 3231
Kläning, U., and Symons, M. C. R., 3269
Knobler, Y. See Frankel, M., 3642
Koczor, I. See Dobó, P., 3461
Layton, A. J. See Clark, J., 3411
Larkworthy, L. F., 3116, 3304
Leonard, M. A. See Belcher, R., 3577
Lescot, E., jun., Buu-Hoï, Ng. Ph., and Xuong, N. D., 3234
Letters, R. See Brown, D. M., 3547
Lewis, D. G. See Edwards, R. L., 3250, 3254
Lewis, J. See Barraclough, C. G., 3552
Lockhart, D. R. See Buchanan, G. L., 3586
Lockhart, I. M. See Ames, A. F., 3388
Lyons, L. E., and Walsh, J. R., 3447
McGowan, J. C., Powell, T., and Raw, R., 3103
McHale, D., Mamalis, P., Mancinkiewicz, S., and Green, J., 3358, 3374
McHale, D. See also Mamalis, P., 3350
McQuillin, F. J., and Ord, W. O., 3169
Malnar, M., and Grdenić, D., 3639
Mamalis, P., Green, J., Marcinkiewicz, S., and McHale, D., 3350
Mamalis, P. See also Green, J., 3362, 3374, McHale, D., 3358, and Marcinkiewicz, S., 3377
Mann, R. S. See Bond, G. C., 3566
Marcinkiewicz, S., McHale, D., Mamalis, P., and Green, J., 3377
Marcinkiewicz, S. See also Green, J., 3362, 3374, McHale, D., 3358, and Mamalis, P., 3350
Markes, J. H. H. See Crofts, P. C., 3610
Markham, E. See Johnson, A. W., 3416
Mathieson, D. W., and Gandhi, V. S., 3650
Mathieson, D. W. See also Arya, V. P., 3623
Maxted, E. B., and Akhtar, S., 3130
Metcalf, W. S., 3654
Middleton, S. See Davies, W., 3544
Millar, I. T. See Carey, J. G., 3144
Miskin, S. F. A. See Bowen, E. J., 3172
Moore, R. C. See Eaborn, C., 3640
Morgan, K. J., 3502
Muggleton, D. F. See French, C. M., 3582
Musgrave, O. C. See Birch, A. J., 3146
Nabi, S. N., and Sheppard, N., 3439
Newbold, G. T. See Allison, W. R., 3335
Nyholm, R. S. See Barraclough, C. G., 3552
Ord, W. O. See McQuillin, F. J., 3169
Osbond, J. M. See Barash, M., 3530, and Brossi, A., 3630
O'Sullivan, J. F. See Barry, V. C., 3217
Overend, W. G. See Ferrier, R. J., 3638
Overton, K. H. See Appel, H. H., 3322
Packer, J. E. See Davies, A. G., 3164
Peacock, T. E., 3241, 3645
Pearson, B. D. See Ward, E. R., 3378, 3635
Peat, S., Turvey, J. R., and Evans, J. M., 3223, 3341
Pengilly, B. W. See Blair, J. M., 3174
Petrow, V., and Williamson, D. M., 3595
Plattner, P. See Brossi, A., 3630
Polgar, N. See Drayson, F. K., 3652
Pope, M. T., Weakley, T. J., and Williams, R. J. P., 3442
Pope, M. T., and Williams, R. J. P., 3579
Powell, A. D. G. See Haws, E. J., 3598
Powell, T. See McGowan, J. C., 3103
Price, R. See Johnson, A. W., 3416
Prout, E. G. See Herley, P. J., 3300
Puckowski, R. T., and Ross, W. A., 3555
Ralph, R. S. See Ames, A. F., 3388
Raw, R. See McGowan, J. C., 3103
Rees, A. H., 3111
Rickards, R. W. See Birch, A. J., 3146
Riley, T. See Bethel, D., 3134
Robertson, A. See Haws, E. J., 3598
Ross, W. A. See Puckowski, R. T., 3555
Ross, W. C. J., and Wilson, J. G., 3616
Rydon, H. N. See Crofts, P. C., 3610
Saint-Ruf, G., Buu-Hoï, Ng. Ph., and Jacquignon, P., 3237
Schnider, O. See Brossi, A., 3630
Shahak, I. See Bergmann, E. D., 3278, 3286
Shannon, K. See Carnie, W. W., 3231
Shaw, K. B. See Johnson, A. W., 3416
Sheppard, N. See Nabi, S. N., 3439
Sheradsky, T. See Frankel, M., 3642
Sims, P., 3648
Singh, S. See Huang, R. L., 3183
Smith, A. C. B. See Harrison, D., 3157
Smith, H. See Birch, A. J., 3146
Stacey, M. See Barker, S. A. 3264
Stedman, G. See Bunton, C. A., 3466
Steele, J. W., Stenlake, J. B., and Williams, W. D., 3289
Stenlake, J. B. See Steele, J. W., 3289
Stephens, R. W. See Bose, J. L., 3314
Sutton, D. A. See Arndt, R. R., 3258
Symons, M. C. R. See Kläning, U., 3269
Thomas, I. M. See Bradley, D. C., 3404
Thompson, A. See Greenwood, N. N., 3474, 3485, 3493, 3643
Tilney-Bassett, J. F., and Waters, W. A., 3123
Tóth, J. See Dobó, P., 3461
Trotman-Dickenson, A. F. See Carnie, W. W., 3231
Turvey, J. R. See Peat, S., 3223, 3341
Twomey, D. See Barry, V. C., 3217
Vincze, I. See Dobó, P., 3461
Vogel, A. I. See Cumper, C. W. N., 3521
Walsh, J. R. See Lyons, L. E., 3447
Ward, E. R., and Pearson, B. D., 3378, 3635
Waters, W. A. See Tilney-Bassett, J. F., 3123
Watt, P. R. See Green, J., 3362
Weakley, T. J. See Pope, M. T., 3442
Webb, R. F., and Duke, A. J., 3627
West, T. S. See Belcher, R., 3577
Wheatley, P. J., 3245
White, J. A. See Carnie, W. W., 3231
Wickens, J. C. See Barash, M., 3530, and Brossi, A., 3630
Wilkins, R. G. See Ellis, P., 3308
Wilkinson, G. See Abel, E. W., 3178
Williams, R. J. P. See Pope, M. T., 3442, 3579
Williams, W. D. See Steele, J. W., 3289
Williamson, D. M. See Petrow, V., 3595
Wilson, J. G. See Ross, W. C. J., 3616
Xuong, N. D. See Lescot, E., jun., 3234
Yeo, O-K. See Huang, R. L., 3190

PAPERS ACCEPTED

The interpretation of the energies of activation of some reactions of aromatic nitro-compounds. By E. F. CALDIN

The preparation of aryl 2-acetamido-2-deoxy-β-D-galactosides. By R. HEYWORTH, D. H. LEABACK, and P. G. WALKER

Submicro-methods for the analysis of organic compounds. Part X. Determination of fluorine. By R. BELCHER, M. LEONARD, and T. S. WEST

Thermodynamics of ion association. Part VI. Some transition-metal sulphates. By V. S. K. NAIR and G. H. NANCOLLAS

Œstrogenic carboxylic acids. Part II. Open-chain analogues of doisynolic acid. By E. R. CLARK and R. D. ROBSON

N-Oxides and related compounds. Part XVI. Infrared spectra of 3-substituted pyridine 1-oxides. By A. R. KATRITZKY, J. A. T. BEARD, and N. A. COATS

Infrared adsorption of heteroaromatic, five-membered, monocyclic nuclei. Part II. 2-Monosubstituted thiophens. By A. R. KATRITZKY and A. J. BOULTON

Purines, pyrimidines, and glyoxalines. Part XIV. The preparation and some reactions of α-amino-α-cyanothioacetamide, leading to 6-mercaptopurines and adenines. By G. SHAW and (in part) D. N. BUTLER

An examination of the Rutaceae of Hong Kong. Part III. The alkaloid, avicine, from *Zanthoxylum avicennae*. By H. R. ARTHUR, (MISS) W. H. HUI, and (in part) (MISS) Y. L. NG

Pyrimidine reactions. Part II. 2-Ethoxy-4-, 4-ethoxy-4-, and 2-hydroxy-5-nitropyrimidine. By D. J. BROWN

Oxidation of organic compounds with quinquevalent vanadium. Part III. The oxidation of cyclohexanol. By J. S. LITTLER and W. A. WATERS

Phenacyl sulphides and related compounds. Part I. The action of alkali on *o*-nitrophenyl phenacyl sulphide. By K. J. MORGAN

The activation of carbon–carbon double bonds by cationic catalysts. Part IX. The dimerisation of 1,1-diphenylethylene in the system benzene–titanium tetrachloride–hydrogen chloride. By A. G. EVANS and E. D. OWEN

Stereochemistry of reduction products of 1-acetyl-2-lycorinone. By Y. NAKAGAWA and S. UYEO

Stereochemistry of lycorenine, homolycorine, pluviine, and their hydrogenation products. By T. KITAGAWA, S. UYEO, and N. YOKOYAMA

The reaction of 1,3,5-trinitrobenzene with aliphatic amines. By R. FOSTER

Acylarylnitrosamines. Part VIII. Reactions of some *o*-methoxynitrosoacetamido-compounds. By Y. ADMAD and D. H. HEY

Synthetical application of activated metal catalysts. Part VIII. The action of degassed Raney nickel on quinoline and some of its derivatives. By W. H. F. SASSE

Steric hindrance in proton transfer to conjugated polyenes. By A. WASSERMANN

Fluorocarbohydrates. Part II. Characterization of (±)-2-deoxy-2-fluoro-glyceric acid and its quinine salts. By P. W. KENT, G. HEBBLETHWAITE, and N. F. TAYLOR

Fluorocarbohydrates. Part III. Reactions of 6-deoxy-6-fluoro-D-galactose. By P. W. KENT, A. MORRIS, and N. F. TAYLOR

Kinetic and structural studies of *trans*-dimeric 3-methyl-3-nitrosobutan-2-one. By L. BATT and B. G. GOWENLOCK

Stationary current–voltage curves for complex electrode processes. By A. C. RIDDIFORD

The synthesis of two dinaphthothiophens. By W. L. F. ARMAREGO

The Ullmann biaryl synthesis. Part I. Atypical products of syntheses of 2,4-dinitrobiphenyl and related compounds. By J. FORREST

The Ullmann biaryl synthesis. Part II. The effect of *m*-dinitrated diluents on the reaction of iodobenzene. By J. FORREST

The Ullmann biaryl synthesis. Part III. The influence of diluents on the reaction of iodobenzene. By J. FORREST

The Ullmann biaryl synthesis. Part IV. The halogen transfer. By J. FORREST

The Ullmann biaryl synthesis. Part V. The influence of ring substituents on the rate of self-condensation of an aryl halide. By J. FORREST

The Ullmann biaryl synthesis. Part VI. The scope and mechanism of the reaction. By J. FORREST

The synthesis and structure of aromatic boron compounds. By J. M. DAVIDSON and C. M. FRENCH

Further experiments with ethylene derivatives of boric acids. By J. A. Blau, W. Gerrard, and M. F. Lappert

Infrared spectra of ethylene and *o*-phenylene derivatives of boric acids. By J. A. Blau, W. Gerrard, M. F. Lappert, B. A. Mountfield, and H. Pyszora

Kinetic and tracer studies of the hydrolysis of phosphourethane. By M. Halmann and A. Lapidot

Boron hydride derivatives. Part II. The separation and identification of some ethylated pentaboranes and decarboranes. By N. J. Blay, J. Williams, and R. L. Williams

Solutions in sulphuric acid. Part XXVI. Cryoscopic measurements by an equilibrium method. By S. J. Bass and R. J. Gillespie

Solutions in sulphuric acid. Part XXVII. The self-dissociation equilibria of sulphuric acid. Values of the equilibrium constants at 10°. By S. J. Bass, R. J. Gillespie, and E. A. Robinson

Ion exchange studies of phosphates. Part IV. Ion exchange and pH-titration studies of copper–triphosphate complexes in solution. By C. Heitner-Wirguin, J. E. Salmon, and E. Mayer

Dimerisation of 2,2-diphenyl- and 2,2-dimethyl-chromen. Part I. By R. Livingstone, D. Miller, and (Miss) S. Morris

Condensation of chlorotriphenylmethane with *ortho*-disubstituted benzenes. Further evidence on the systematic difference of activation of *ortho*- and *para*-directing groups. By G. Chuchani

Solutions in sulphuric acid. Part XXVIII. Osmotic coefficients of some electrolyte solutions. By S. J. Bass, R. J. Gillespie, and J. V. Oubridge

Solutions in sulphuric acid. Part XXIX. Densities and apparent molar volumes of some electrolyte solutions. By R. H. Flowers, R. J. Gillespie, and E. A. Robinson

Organophosphorus compounds of sulphur and selenium. Part XIII. Action of hydrogen sulphide on diaryl phosphorochloridites. New synthesis of dialkyl and diaryl thiophosphites and tetra-alkyl thiopyrophosphites. By Cz. Krawiecki and J. Michalski

Polarographic reduction of aromatic hydrocarbons and carbonyl compounds in dimethylformamide in the presence of proton donors. By P. H. Given and M. E. Peover

Investigation of carbonyl groups in solvent extracts of coals. By P. H. Given and M. E. Peover

Binding of cyclo-octatetraene to metal atoms. Simple theoretical consideration. By F. A. Cotton

Acid-catalysed rearrangements of alkyl aryl ethers. Part IV. Rearrangement of alkyl tolyl ethers by aluminium chloride. By M. J. S. Dewar and N. A. Puttnam

Chlorine atom exchange between antimony trichloride and trimethylchlorosilane in benzene and hexane. Part I. Apparatus and techniques. By A. F. Reid and R. Mills

Amino-oxy-derivatives. Part I. Some α-amino-oxy-acids and α-amino-oxy-hydrazides. By D. McHale, J. Green, and P. Mamalis

Amino-oxy-derivatives. Part II. Some derivatives of *N*-hydroxydiguanide. By P. Mamalis, J. Green, and D. McHale

The kinetics of alkyl–oxygen fission in ester hydrolysis. Part VII. *p*-Methoxydiphenylmethyl benzoate. By S. R. Johns and V. R. Stimson

Nuclear magnetic resonance in polymethylene and polyethylene. By M. J. Herring and J. A. S. Smith

The periodate oxidation of the inositols. By G. R. Barker

The infrared spectrum of thiocyanogen and thiocyanogen halides. By (Mrs.) M. J. Nelson and A. D. E. Pullin

Kinetics and mechanism of the decomposition of complex cyanides of iron(II) and molybdenum(IV). By S. Asperger, I. Murati, and D. Pavlovic

Triterpenoids from lignite. By R. Ikan and J. McLean

Aspects of stereochemistry. Part III. Acid and basic hydrolysis of some diol cyclic sulphates and related compounds. By J. S. Brimacombe, A. B. Foster, E. B. Hancock, W. G. Overend, and M. Stacey

Potential antipurines. Part III. Some 9-dialkylaminoalkyl-purines and -8-azapurines. By J. H. Lister and G. M. Timmis

Bicyclo[2,2,1]heptadiene in the Diels–Alder reaction. By K. Mackenzie

The heat of sublimation and the metal–metal bond energy in $Mn_2(CO)_{10}$. By F. A. Cotton and R. R. Monchamp

Structure and reactivity of the oxyanions of transition metals. Part VII. Kinetics and mechanism of the alkaline decomposition of per-ruthenate. By A. Carrington and M. C. R. Symons

Studies in stereochemical structure. Part XIII. Derivatives of the hydratropic acids and hydratropic alcohols. By R. Roger and D. G. Neilson

Solvolysis of dibenzyl *trans*-2-hydroxycyclohexyl phosphate. By D. M. Brown and N. K. Hamer
Some reactions of the radical 2,4,6-tri-t-butylphenoxyl. By J. C. McGowan and T. Powell.
Experimental studies of solution processes. Part IV. Spectrophotometric studies of the system: iodine–nitromethane–carbon tetrachloride. By P. A. D. de Maine and W. C. Ahlers
Atom and bond populations in nitrogen heterocyclics. By T. E. Peacock
Reactions of some diaryl sulphides. By I. L. Finar and A. J. Montgomery
Intramolecular reactions of amides. Part II. Cyclisation of amides of ω-bromo-carboxylic acids. By C. J. M. Stirling
The effect of deuteration on electron distribution and energy of conjugated molecules. Part III. LCAO–MO treatment of ethylcarbonium ion and its methyl-deuterated analogue. By (Mrs.) A. Ron, E. A. Halevi, and R. Pauncz
Free-radical substitution in aliphatic compounds. Part II. The halogenation of the n-butyl halides. By P. S. Fredricks and J. M. Tedder
Perylene syntheses. Part II. Synthesis of 2,8- and 3,9-dimethylperylene. By (Miss) J. M. Anderson, A. D. Campbell, G. W. Emerson, and J. Murray
Structure and reactivity of the oxy-anions of transition metals. Part VIII. Acidities and spectra of protonated oxyanions. By N. Bailey, A. Carrington, K. A. J. Lott, and M. C. R. Symons
Structure and reactivity of the oxy-anions of transition metals. Part IX. Electronic structure. By A. Carrington and M. C. R. Symons
Some derivatives of 5,6,7,8-tetrahydrophenanthridine. By B. L. Hollingsworth and V. Petrow
Physicochemical studies on starches. Part XXI. Observations on Z-enzyme. By W. Banks, C. T. Greenwood, and I. G. Jones
Organophosphorus compounds of sulphur and selenium. Part XIII. The reaction of organic diselenides with trialkyl phosphites. By J. Michalski and J. Wieczorkowski
Polarographic study of manganese, technetium, and rhenium. By R. Colton, J. Dalziel, W. P. Griffith, and G. Wilkinson
Tricarbonylchromium derivatives of aromatic compounds; some discrepancies. By W. R. Jackson, B. Nicholls, and M. C. Whiting
Nuclear resonance spectra of the polymorphic forms of glycerides. By D. Chapman, R. E. Richards, and R. W. Yorke
Spectroscopic studies of phenols. Effect of substituents on hydrogen bonding. By N. A. Puttnam
Some racemisation data for compounds owing their optical activity to restricted rotation. By D. M. Hall and M. M. Harris
The alkaloids of *Kreysigia multiflora* Reichb. Part I. Isolation. By G. M. Badger and R. B. Bradbury
The mechanism of hydrolysis of phosphonochloridates and related compounds. Part I. The effect of substituents. By R. F. Hudson and L. Keay
The mechanism of hydrolysis of phosphonochloridates and related compounds. Part II. The effect of the solvent. By R. F. Hudson and L. Keay
Methylation and periodate oxidation studies of the alkali-stable polysaccharide of sugar-beet pectin. By L. Hough and D. B. Powell
The desorption of alcohols from metal oxides. Part I. Ethanol and propan-2-ol. By D. J. Wheeler, P. W. Darby, and C. Kemball
Diboron tetrachloride–olefin compounds. Part I. Some properties of diboron tetrachloride–ethylene. By A. K. Holliday and A. G. Massey
The photolysis of triethylamine and the reactions of methyl radicals with triethylamine and diethylamine. By P. J. Kozak and H. Gesser
The preparation of some β-diketones from copper complexes and nitrobenzoyl chlorides. By W. J. Barry
The constitution of aspidospermine. Part IV. By G. F. Smith and J. †. Wróbel
Researches on acetylenic compounds. Part LXII. The preparation and some synthetical applications of penta-1,2,4-triene and penta-1,2-dien-4-yne. By E. R. H. Jones, H. H. Lee, and M. C. Whiting
Boron hydride derivatives. Part III. Electrophilic substitution in petaborane and decaborane. By N. J. Baly, I. Dunstan, and R. L. Williams
The structure of sorbilcillin hydrogen bonding in *o*-hydroxyaryl alkenyl ketones. By J. Smith and R. H. Thomson
Heterocyclic fluorine compounds. Part IV. Monofluoroindazoles. By I. K. Barben and H. Suschitzky

XUM

Chemistry of the higher fungi. Part X. Further polyacetylenic derivatives of n-decane from various Basidiomycetes. By J. N. Gardner, E. R. H. Jones, P. R. Leeming, and J. S. Stephenson

Oxygen exchange between nitrous acid and water. Part II. Exchange in acetate buffers. By C. A. Bunton and M. Masui

The thermal isomerisation of methyl geranate and dihydromyrcene. By G. A. Howard and R. Stevens

The electronic spectra of *N*-heteroaromatic systems. Part VI. The $\pi \longrightarrow \pi$ transitions of the monocyclic amino- and mercapto-azines. By S. F. Mason

Chemistry of hop constituents. Part XIV. 2,4-Diacetyl-3,4-dihydroxyl-5-methylcyclopent-2-enone, and analogue of isohumulone A. By P. M. Brown and G. A. Howard

Conjugated cyclic hydrocarbons and their heterocyclic analogues. Part II. The condensation of azulenes with homocyclic and heterocyclic aromatic aldehydes in the presence of perchloric acid. By E. C. Kirby and D. H. Reid

Spasmolytics derived from xanthene. Part II. By A. A. Goldberg and A. H. Wragg

Reaction of α-cyanobenzyl bromide with some nucleophilic reagents. By J. E. Banfield

The synthesis of 8-methylbenzo[*k*]fluoranthene and of dibenzo[*b*,*k*]fluoranthene. By Ng. Ph. Buu-Hoï and Denise Lavit

Pyrones. Part I. Methyl ethers of tautomeric hydroxypyrones and the structure of yangonin. By J. D. Bu'Lock and H. G. Smith

Infrared absorption of substituents in aromatic systems. Part IV. Ethyl *N*-arylurethanes. By A. R. Katritzky and R. A. Jones

Synthetical studies relating to colchicine. Part II. Diethyl 1,2-benzocyclohepta-1,3-diene-4-acetate-3-β-propionate and its 3′,4′,5′-trimethoxy-analogue. By T. A. Crabb and K. Schofield

Ipecacuanha alkaloids. Part V. Stereospecific synthesis of (+)-*O*-methylpsychotrine and (−)-emetine. By A. R. Battersby and J. C. Turner

The basic properties, infrared spectra, and structures of triphenylamine and tri-*p*-tolylamine. By R. D. W. Kemmitt, R. H. Nuttal, and D. W. A. Sharp

An accurate determination of the crystal structure of thioacetamide. By M. R. Truter

Diphenylenes. Part IV. Bond structure. By Wilson Baker, J. F. W. McOmie, D. R. Preston, and V. Rogers

The reaction between 2,4-dinitrotoluene and phthalic anhydride in dimethylaniline. By K. J. Clark and G. I. Fray

The formation of aromatic hydrocarbons at high temperatures. Part VI. The pyrolysis of tetralin. By G. M. Badger and R. W. L. Kimber

The reaction of *o*-phenylenediamine with αβ-unsaturated acids and with β-keto esters. By J. Davoll

Some *N*-substituted 2-oxobenzimidazolines. By J. Davoll and D. H. Laney

The methylation of adenosins and adenylic acid. By P. Brookes and P. D. Lawley

The Stobbe condensation. Part II. The cyclisation of methyl hydrogen *cis*-3 : 4-methylenedioxyphenyl- and methyl hydrogen *cis*-3 : 4-dimethoxyphenylitaconate to the corresponding polysubstituted naphthalene derivatives. By L. S. El-Assal and (Mrs.) S. A. M. El-Wahhab

Amine compounds of the transition elements. Part IV. The reaction of tantalum(v) halides with some aliphatic amines. By P. J. H. Carnell and G. W. A. Fowles

The replacement of the diazonium by the nitro-group. Part VI. Further simplifications in technique, and the improved preparation of *o*- and *p*-dinitrobenzenes. By E. R. Ward, C. D. Johnson, and J. C. Hawkins

Raman spectra of the hexamethyl compounds of silicon, germanium, and tin. By M. P. Brown, E. Cartmell, and G. W. A. Fowles.

A synthesis of irone. By D. H. R. Barton and M. Mousseron-Canet

Radiation chemistry of carbohydrates. Part III. The effect of gamma radiation on aqueous solutions of D-fructose. By G. O. Phillips and G. J. Moody

Radiation chemistry of carbohydrates. Part IV. The effect of gamma radiation on aqueous solution of sucrose. By G. O. Phillips and G. J. Moody

Photochemical transformations. Part VII. Stereospecificity in an irradiation process. By D. H. R. Barton, R. Bernasconi, and J. Klein

Urea and related compounds. Part VII. Isomerisation of 1,*O*-dimethyl-2-thioisobiuret to 1,*S*-dimethyl-2-thioisobiuret. By F. Kurzer and S. A. Taylor

The synthesis of a β-batyl (glycerol 2-octadecyl ether) analogue of cephalin, and melting-point data for batyl, chimyl, β-batyl, β-chimyl alcohols and derivatives. By T. H. Bevan and T. Malkin

630. *The Rates of Reaction of αα-Diphenyl-β-picrylhydrazyl with Certain Amines and Phenols.*

By J. C. McGowan, T. Powell, and R. Raw.

The reactions of primary arylamines with αα-diphenyl-β-picrylhydrazyl in carbon tetrachloride have been found to obey the third-order law:

Rate of disappearance of hydrazyl = k_3[Hydrazyl]^2[Aniline]

A number of other amines and phenols gave a second-order reaction with the hydrazyl. Alcohols and t-butylamine did not, however, react at an appreciable rate. The effects of substituents on the reaction with phenols are similar to their effects on reactions in which a carbonium ion is formed adjacent to a phenyl ring. Bulky groups *ortho* to the phenolic hydroxyl hinder the reaction. The reactions of *p*-aminobenzonitrile, *m*- and *p*-nitroaniline, *p*-aminobenzophenone, *NN*-dimethyl-*p*-nitroaniline, and *m*- and *p*-nitrophenol were greatly accelerated by light, and were then of first order with respect to αα-diphenyl-β-picrylhydrazyl and of zero order with respect to the amine or phenol.

Braude, Brook, and Linstead [1] found that hydrogen transfer took place between the stable free radical αα-diphenyl-β-picrylhydrazyl and a number of quinols, catechols, hydroaromatic compounds, and aromatic amines. They measured the rates of reactions of the hydrazyl with some hydroaromatic compounds in dioxan, found that the reactions obeyed approximately the third-order law (rate = k_3[Hydrazyl]^2[Donor]), and showed that the energies of activation were between 20 and 35 kcal. per mole. Russell [2] studied the reactions between αα-diphenyl-β-picrylhydrazyl and alkanethiols in benzene and found that the rates of disappearance of the hydrazyl could be expressed as $2k$[Hydrazyl][Thiol]. At 60°, the values of k varied from 0·23 l. mole^{-1} min.$^{-1}$ for t-butanethiol to 4·56 for hexane-1-thiol and the activation energy was in every case about 15 kcal. per mole. The products of the reactions of thiophenol, butanethiol, ammonia, hydrazine, hydroxylamine, methylamine, n-butylamine, isopropylamine, and diethylamine with αα-diphenyl-β-picrylhydrazyl were investigated [3] and in every case high yields of αα-diphenyl-β-picrylhydrazine were obtained. The reactions between αα-diphenyl-β-picrylhydrazyl and some aromatic secondary amines have also been studied.[4,5]

Homolytic transfers of hydrogen atoms from donors to free radicals are of considerable interest in connexion with termination and transfer processes in chain reactions involving radicals. Autoxidations are important examples of such reactions. The propagation reactions are

$$R\cdot + O_2 \longrightarrow RO_2\cdot$$
$$RO_2\cdot + RH \longrightarrow R{\cdot}O{\cdot}OH + R\cdot$$

The termination reaction brought about by a hydrogen donor AH is usually considered to be $RO_2\cdot + AH \longrightarrow R{\cdot}O{\cdot}OH + A\cdot$. Hammond, Sen, and Boozer,[6] however, consider that this mechanism is incorrect. They found that with *N*-methylaniline and with phenol as inhibitors the initial oxidation rates for cumene and tetralin catalyzed by azodi-isobutyronitrile were inversely proportional to the square roots of the inhibitor concentrations, *i.e.*, the rate of termination was proportional to [Alkylperoxy-radical]^2[Inhibitor]. The reaction therefore resembles the third-order reactions [1] of αα-diphenyl-β-picrylhydrazyl with hydroaromatic compounds. Moreover, no kinetic isotope effect was found when *N*-deutero-*N*-methylaniline and -diphenylamine were compared with the undeuterated

[1] Braude, Brook, and Linstead, *J.*, 1954, 3574.
[2] Russell, *J. Phys. Chem.*, 1954, **58**, 438.
[3] Brook, Anderson, and Patot, *Canad. J. Chem.*, 1958, **36**, 159.
[4] Hazell and Russell, *Canad. J. Chem.*, 1958, **36**, 1729.
[5] Kuz'minskii and Angert, *Doklady Akad. Nauk S.S.S.R.*, 1954, **96**, 1187.
[6] Hammond, Sen, and Boozer, *J. Amer. Chem. Soc.*, 1955, **77**, 3239.

amines. Hammond, Sen, and Boozer suggest that the alkylperoxy-radicals react reversibly with the inhibitor to give a complex which is then destroyed in an irreversible reaction with a second alkylperoxy-radical. Bickel and Kooyman [7] consider that the usual mechanism is adequate to explain the inhibition of the autoxidation of dihydroanthracene by 2,4,6-trialkylphenols. They [8] treated 4-methyl-2,6-di-t-butylphenol with αα-diphenyl-β-picrylhydrazyl in toluene and found the reaction was of second order: $k = 4{\cdot}7$ and $6{\cdot}3$ l. mole^{-1} min.$^{-1}$ at 20° and 30°, respectively. Some reactions of radicals with hydrogen donors appear to be of second order whilst others are of third order. It is not clear what factors determine the order or the rates of the reactions. αα-Diphenyl-β-picrylhydrazyl is a very convenient radical and since a further study of its reactions with amines and phenols appeared to be worthwhile, the work described below was carried out.

Experimental

αα-Diphenyl-β-picrylhydrazyl, prepared as by Poirier, Kahler, and Benington,[9] was dissolved in carbon tetrachloride. The solution was placed in a three-necked litre flask fitted with a reflux condenser, and carbon dioxide bubbled through it. The flask was placed in a thermostat and when the solution had reached the bath-temperature a weighed quantity of the purified amine or phenol was introduced either alone or in a small amount of carbon tetrachloride, the mixture made up to volume, and the reaction carried out under carbon dioxide. Samples were taken out at intervals and the optical density was measured as quickly as possible in an EEL absorptiometer with Filter No. 604. The concentrations (moles per l.) of αα-diphenyl-β-picrylhydrazyl were found by multiplication of the optical densities for a 1 cm. thick cell by $8{\cdot}58 \times 10^{-5}$. For the slowest reactions, cells 0·5 cm. thick were used, and, for fast reactions, cells 4 cm. or 10 cm. thick. The products were always somewhat coloured and the absorptiometer reading was corrected for this. The reaction was run practically to completion and the colour corresponding to total conversion into the product was obtained. It was then assumed that the same coloured products were produced throughout the reaction in proportion to the amount of αα-diphenyl-β-picrylhydrazyl which had disappeared. Details of two typical runs, one of third order and the other of second order, are given below. $D_{obs.}$ and $D_{corr.}$ are the observed and the corrected optical density, the latter being proportional to $(a - x)$, the hydrazyl concentration; $k_2 = x/t(a - x)$, and $k_1 = (1/t) \log_e a/(a - x)$.

m-*Toluidine* ($4{\cdot}900 \times 10^{-3}$ *mol. per l.*) *in carbon tetrachloride at* 40·8° (Cell 4 cm. thick.)

Time (min.)	$D_{obs.}$	$D_{corr.}$	10^3k_2	Time (min.)	$D_{obs.}$	$D_{corr.}$	10^3k_2	Time (min.)	$D_{obs.}$	$D_{corr.}$	10^3k_2
0	0·96	0·96	—	55	0·69	0·62	1·00	210	0·44	0·30	1·05
15	0·86	0·83	1·04	75	0·63	0·54	1·04	385	0·35	0·19	1·05
25	0·80	0·76	1·05	95	0·59	0·49	1·01	1200	0·20	0	—
35	0·76	0·71	1·01	115	0·55	0·44	1·03	Average : $k_2 = 1{\cdot}03 \times 10^{-2}$			

$$k_3 \text{ for third-order reaction} = \frac{x}{(a-x)t} \times \frac{1}{a[m\text{-Toluidine}]}$$

$$= 1{\cdot}03 \times 10^{-2} \times \frac{4}{4{\cdot}900 \times 10^{-3} \times 8{\cdot}58 \times 10^{-5} \times 0{\cdot}96}$$

$$= 1{\cdot}02 \times 10^{5} \text{ l.}^2 \text{ mole}^{-2} \text{ min.}^{-1}$$

2,4-*Dimethyl*-6-2′-*methylcyclohexylphenol* ($4{\cdot}767 \times 10^{-5}$ *mol. per l.*) *at* 20·0° *in carbon tetrachloride.* The cell used was 4 cm. thick. Results are in Table 1.

$$k \text{ for second-order reaction} = \frac{1}{t} \log_e \frac{a}{a-x} \times \frac{1}{[\text{Phenol}]}$$

$$= 2{\cdot}35 \times 10^{-2} \times \frac{1}{4{\cdot}767 \times 10^{-5}}$$

$$= 493 \text{ l. mole}^{-1} \text{ min.}^{-1}$$

[7] Bickel and Kooyman, *J.*, 1956, 2215; 1957, 2217.
[8] *Idem*, *ibid.*, 1957, 2415.
[9] Poirier, Kahler, and Benington, *J. Org. Chem.*, 1952, **17**, 1437.

In Table 2 are given the results of experiments in which primary aromatic amines reacted with αα-diphenyl-β-picrylhydrazyl in carbon tetrachloride solutions. The reactions are all calculated as third order, *i.e.*:

$$\text{Rate of disappearance of hydrazyl} = k_3[\text{Hydrazyl}]^2[\text{Amine}]$$

All the reactions were found to be of the second order with respect to hydrazyl. In a number of cases, different concentrations of amine were used and the reaction was found to be of the first order with respect to the amine: for example, at 41·0° with *p*-chloroaniline at $1{\cdot}570 \times 10^{-2}$ and $7{\cdot}85 \times 10^{-3}$ mole per l., the values of k_3 were $1{\cdot}83 \times 10^4$ and $1{\cdot}87 \times 10^4$ l.^{2} mole^{-2} min.$^{-1}$.

TABLE 1.

Time (min.)	$D_{obs.}$	Corr. D proportional to hydrazyl concn. $(a-x)$	$\frac{10^2}{t}\log_e\frac{a}{a-x}$	Time (min.)	$D_{obs.}$	Corr. D proportional to hydrazyl concn. $(a-x)$	$\frac{10^2}{t}\log_e\frac{a}{a-x}$
0	0·85	0·85 (propl. to a)	—	36	0·40	0·37	2·30
5	0·76	0·755	2·37	41	0·35	0·32	2·38
10	0·68	0·67	2·38	46	0·32	0·29	2·34
15	0·61	0·595	2·38	56	0·26	0·22	2·39
21	0·54	0·52	2·34	116	0·10	0·053	2·39
26	0·48	0·455	2·40	600	0·05	0	—
31	0·44	0·415	2·31				Average = 2·35

TABLE 2. *Reactions of αα-diphenyl-β-picrylhydrazyl with primary aromatic amines.**

Amine	Temp. (°K)	k_3	$RT\log_e k_3$	14Q for Ph group [10]
m-$C_6H_4Cl{\cdot}NH_2$	292·1	$4{\cdot}72 \times 10^2$	3·53	8·0
	314·1	$5{\cdot}70 \times 10^3$	5·36	8·0
	333·1	$9{\cdot}91 \times 10^4$	7·58	8·0
	351·1	$2{\cdot}38 \times 10^5$	8·61	8·0
m-$C_6H_4Br{\cdot}NH_2$	292·6	$5{\cdot}37 \times 10^2$	3·64	7·8
	314·1	$2{\cdot}82 \times 10^3$	4·92	7·8
	332·1	$7{\cdot}74 \times 10^4$	7·40	7·8
	351·1	$2{\cdot}32 \times 10^5$	8·59	7·8
p-$C_6H_4Cl{\cdot}NH_2$	294·6	$2{\cdot}34 \times 10^3$	4·50	7·4
	314·1	$1{\cdot}85 \times 10^4$	6·09	7·4
	332·1	$2{\cdot}72 \times 10^5$	8·23	7·4
	351·1	$1{\cdot}23 \times 10^6$	9·76	7·4
$C_6H_5{\cdot}NH_2$	273·1	$1{\cdot}43 \times 10^3$	3·90	6·6
	294·1	$5{\cdot}91 \times 10^3$	5·03	6·6
	314·1	$6{\cdot}10 \times 10^4$	6·84	6·6
	332·3	$3{\cdot}18 \times 10^5$	8·33	6·6
m-$C_6H_4Me{\cdot}NH_2$	273·1	$2{\cdot}40 \times 10^3$	4·18	6·3
	293·1	$1{\cdot}51 \times 10^4$	5·56	6·3
	313·9	$1{\cdot}01 \times 10^5$	7·14	6·3
p-$C_6H_4Me{\cdot}NH_2$	273·1	$5{\cdot}51 \times 10^3$	4·64	6·2
	293·1	$3{\cdot}70 \times 10^4$	6·02	6·2
	314·1	$2{\cdot}92 \times 10^5$	7·82	6·2

* k_3 = third-order rate constant (l.^{2} mole^{-2} min.$^{-1}$).

TABLE 3. *Reactions of αα-diphenyl-β-picrylhydrazyl with amines.*

Amine	Temp.	k (l. mole^{-1} min.$^{-1}$)	Amine	Temp.	k (l. mole^{-1} min.$^{-1}$)
t-Butylamine ...	76°	<0·0001	Morpholine	77°	1·33
n-Butylamine	77	0·90	*N*-Methylpyrrolidine	76	4·33
Triethylamine ...	40	0·48	Dimethylaniline	40	2·31
	58	0·80		77	5·25
	77	1·62			

In chloroform k for n-butylamine was 0·12 at 20° and 0·37 at 62°.

p-Nitroaniline, *m*-nitroaniline, *p*-aminobenzonitrile, and *p*-aminobenzophenone were found to react with αα-diphenyl-β-picrylhydrazyl only very slowly in the dark but in the light beam of the EEL absorptiometer the reactions all proceeded quite readily. In the light, the reactions were of the first order with respect to αα-diphenyl-β-picrylhydrazyl and of zero order with respect to the amine. The reactions of *NN*-dimethyl-*p*-nitroaniline and *m*- and *p*-nitrophenol with αα-diphenyl-β-picrylhydrazyl were also very slow in the dark and comparatively fast in the light.

[10] McGowan, *J. Soc. Chem. Ind.*, 1949, **68**, 253.

XUM

In Table 3 are given results of experiments in which some other amines reacted with αα-diphenyl-β-picrylhydrazyl in carbon tetrachloride. The reactions were all found to be of the first order with respect to the hydrazyl. In the case of morpholine at 77°, the reaction was shown to be of the first order with respect to the amine (k was 1·36 at 2·10 × 10^{-2} mole per l. and 1·30 at 8·06 × 10^{-2} mole per l. of morpholine) and the reactions were assumed to be of the first order with respect to the other amines so that

$$\text{Rate of disappearance of hydrazyl} = k[\text{Hydrazyl}][\text{Amine}]$$

The activation energies for these reactions are about 5 kcal. per mole.

TABLE 4. *Rate constants, k, for the bimolecular reactions of phenols with αα-diphenyl-β-picrylhydrazyl in carbon tetrachloride at about 20° compared with various measures of antioxidant activity and of steric hindrance.*

	1	2	3	4	5	6	7
No phenol	—	—	45	—	0	—	—
Phenols with a free ortho-*position*							
4-Chlorophenol	1·1 (19·0°)	—	45	—	—	—	—
Phenol	4·3 (19·6°)	83	75	0·92	0	1·0	0·25
3,5-Dimethylphenol	46 (20°)	545	—	0·86	25	0·8	—
2-Methylphenol	47 (19·5°)	522	135	0·85	15	0·7	—
4-Methylphenol	55 (19·0°)	291	210	0·84	—	1·4	0·28
4-(1,1,3,3-Tetramethylbutyl)phenol	76 (18·3°)	—	—	—	—	1·0	0·27
4-t-Butylphenol	83 (20·0°)	464	210	0·84	—	0·9	0·20
2,3-Dimethylphenol	100 (18·0°)	591	—	0·85	25	1·0	—
2,5-Dimethylphenol	106 (17·6°)	—	285	0·82	25	1·0	—
β-Naphthol	377 (19·0°)	830	330	0·70	—	—	—
2,4-Di-t-butylphenol	520 (18·0°)	1430	—	0·76	—	1·2	—
2,4-Dimethylphenol	789 (18·4°)	1310	420	0·76	50	0·8	0·19
4-Benzyloxyphenol	7000 (18·0°)	1710	—	0·71	80	—	—
α-Naphthol	8000 (15·5°)	3950	2250	0·68	150	—	—
4-Methoxyphenol	14,000 (21·0°)	—	—	0·71	85	—	0·24
4-Methoxy-3-t-butylphenol	~20,000 (20·8°)	—	—	0·64	150	—	—
4-Methoxy-2-(1,1,3,3-tetramethylbutyl)-phenol	~40,000 (19·5°)	—	—	0·64	295	—	—
4-Methoxy-2,5-di-t-butylphenol	~60,000 (16·0°)	—	—	0·63	160	—	—
4-t-Butylcatechol	>100,000 (18·6°)	—	—	—	—	—	—
4-Methylcatechol	>100,000 (18·0°)	—	—	—	—	—	—
2,6-*Dimethylphenols*							
2,6-Dimethylphenol	117 (19·0°)	1110	420	0·76	30	2·3	0·09
2,4,6-Trimethylphenol	1350 (20·1°)	2070	—	0·67	100	3·6	0·08
2-*Methylphenols with a bulky group in* 6-*position*							
2,4-Dimethyl-6-t-butylphenol	323 (18·5°)	3320	—	0·65	125	15·0	0·04
2,4-Dimethyl-6-(1,1,3,3-tetramethylbutyl)-phenol	350 (19·0°)	—	—	0·66	145	13·8	0·03
2,4-Dimethyl-6-2′-methylcyclohexylphenol	466 (19·3°)	—	—	—	—	10·4	—
Phenols with bulky groups in both 2- *and* 6-*positions*							
2,4,6-Tri-t-butylphenol	22 (19·2°)	1430	—	0·69	85	220	0·003
4-Methyl-2,6-di-t-butylphenol	31 (18·3°)	1990	—	0·68	70	156	0·008
4-Ethyl-2,6-di-t-butylphenol	32 (17·0°)	—	—	0·72	105	151	—

In Table 4 are given results of experiments in which phenols were treated with αα-diphenyl-β-picrylhydrazyl in carbon tetrachloride. The rate constants (average) for the bimolecular reactions are given in col. 1. These reactions were carried out at two phenol concentrations, one approximately four times the other, and the values of k were always in good agreement.

In col. 2 are shown the relative rates calculated [11] for the capture of tetralyl peroxide radicals at 50° by the phenols. In col. 3 are induction periods found [12] for the oxidation of gasoline containing 0·01% of phenol, in oxygen under pressure at 100°. Col. 4 gives the

[11] Davies, Goldsmith, Gupta, and Lester, *J.*, 1956, 4926.
[12] Egloff, Morrell, Lowry, and Dryer, *Ind. Eng. Chem.*, 1932, **24**, 1375.

relative oxidation potentials of phenols in 50% alcohol extrapolated to zero pH.[13] Col. 5 gives figures from Penketh [13] for the increase in induction period caused by the addition of 10^{-5}M-phenol to fully saturated petrol in the A.S.T.M. bomb test (D 525 — 49). In col. 6 are the values (see p. 3110) of k(calc.)/k(obs.) for alkyl-phenols, and in col. 7 the differences in wavelength (microns) of the O–H infrared absorption between a dilute solution in carbon tetrachloride and a concentrated solution or melt.[14]

The reactions of some phenols with αα-diphenyl-β-picrylhydrazyl were studied in carbon tetrachloride at temperatures other than around 20° and in other solvents. The results are listed in Table 5 and show that the activation energies are between 5 and 10 kcal. per mole.

TABLE 5. *Further rate constants (k in l. mole^{-1} min.$^{-1}$) for the bimolecular reactions of phenols with αα-diphenyl-β-picrylhydrazyl.*

Phenol	Temp.	Solvent	k	Phenol	Temp.	Solvent	k
p-Cresol	2°	CCl_4	23	2,4,6-Tri-t-butylphenol	1°	CCl_4	9
	39	,,	166		40	,,	46
	77	,,	1015		77	,,	210
	3	$CHCl_3$	7·6	4-Methyl-2,6-di-t-butyl-phenol	1	,,	18
	18·3	,,	19		19·6	PhMe	17
	31	,,	45		32	,,	26
2,4-Dimethyl-6-2′-methyl-cyclohexylphenol	0	CCl_4	263				

Toluene, sulphur, phthalimide, triphenylmethane, methanol, ethanol, and propan-2-ol did not react at an appreciable rate with αα-diphenyl-β-picrylhydrazyl in carbon tetrachloride at 77°.

Discussion

The effects of charged atoms on the free energies of ionization ($\Delta G_0 = -\boldsymbol{R}T \log_e K$) of protons in acidic molecules and on the free energies of other reactions involving transfers of electrical charges have been discussed elsewhere.[15] Phenyl and other groupings give effects resembling those of charges and each grouping may be allotted an "effective charge" (Q) which may be defined as the hypothetical charge which would be required to give the same effect as the grouping (Y). The following relation may be written for the effect upon a given equilibrium of substitution of different groupings (Y) for hydrogen:

$$\Delta G^\circ = -\boldsymbol{R}T \log_e K = \Delta G_H^\circ + BQ$$

where ΔG_H° is the value of ΔG° when Y is hydrogen; and B may be equated with $14/2^n$, where n depends on the structure separating the group Y from the atom involved in the change of charge. In the case of the ionization of a proton, it equals the number of atoms between Y and the dissociating proton if all these atoms are saturated, so that with dilute aqueous solutions at 25°

for $\quad YOH \longrightarrow YO^- + H^+ \qquad \Delta G^\circ = 19{\cdot}9 - 14Q$

and for $\quad Y{\cdot}NH_3^+ \longrightarrow Y{\cdot}NH_2 + H^+ \qquad \Delta G^\circ = 12{\cdot}9 - 14Q$

The treatment is not confined to 25° and can be applied to other media besides water and for the reactions

$$YO\cdot + e \longrightarrow YO^-$$

and

$$Y{\cdot}\dot{N}H_2^+ + e \longrightarrow Y{\cdot}NH_2$$

one would expect $\Delta G^\circ = \Delta G_H^\circ - 14Q$.

The effect of groupings and charges upon velocity constants (k) has been found to be similar to the effects upon equilibria, and $\boldsymbol{R}T \log_e k + BQ$ values are constant for

[13] Penketh, *J. Appl. Chem.*, 1957, **7**, 512.
[14] Sears and Kitchen, *J. Amer. Chem. Soc.*, 1949, **71**, 4110.
[15] McGowan, *Nature*, 1947, **159**, 644; 1951, **168**, 601; *Chem. and Ind.*, 1948, 632; 1951, 601; and ref. 10.

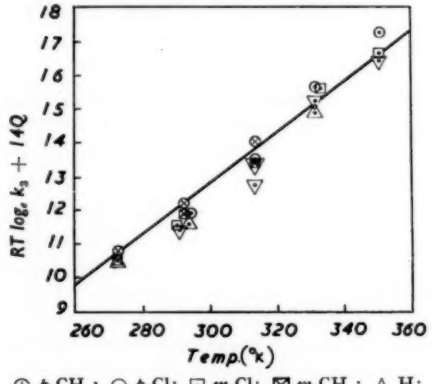
reactions which all involve the same change of charge. The values of Q for substituted phenyl groups listed previously [10] are used here. The equation involving B and Q links reactions in the aromatic series with those in the aliphatic series and indicates the changes in charges more directly than does the well-known equation of Hammett.[16]

The reactions of substituted anilines with αα-diphenyl-β-picrylhydrazyl in carbon tetrachloride have been found to obey the third-order law:

$$\text{Rate of disappearance of hydrazyl} = k_3[\text{Hydrazyl}]^2[\text{Aniline}]$$

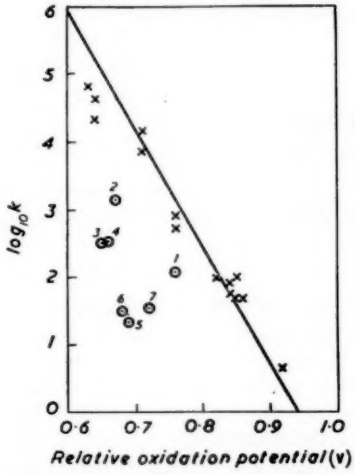
and $\boldsymbol{R}T \log_e k_3 + 14Q$ is a constant for all the anilines at any one temperature. Now if k_3

FIG. 1. *Reaction of αα-diphenyl-β-picrylhydrazyl with primary aromatic amines.*



⊕ *p*-CH_3; ⊙ *p*-Cl; ⊡ *m*-Cl; ⊠ *m*-CH_3; △ H; ▽ *m*-Br.

FIG. 2. *Relative oxidation potentials and $\log_{10} k$ values for phenols.*



1, 2,6-Dimethylphenol. 2, 2,4,6-Trimethylphenol. 3, 4,6-Dimethyl-1-t-butylphenol. 4, 2,4-Dimethyl-6-(1,1,3,3-tetramethylbutyl)phenol. 5, 2,4,6-Tri-t-butylphenol. 6, 4-Methyl-2,6-di-t-butylphenol. 7, 4-Ethyl-2,6-di-t-butylphenol.

is equal to $Ae^{-E/\boldsymbol{R}T}$; $\boldsymbol{R}T \log_e k_3 = \boldsymbol{R}T \log_e A - E$ for any one aniline at any temperature; and $\boldsymbol{R}T \log_e k_3 + 14Q - \boldsymbol{R}T \log_e A =$ a constant for all anilines at all temperatures. In Fig. 1, values of $\boldsymbol{R}T \log_e k_3 + 14Q$ are plotted against T and it will be seen that the points fall close to the straight line which corresponds to

$$\boldsymbol{R}T \log_e k_3 + 14Q = 0{\cdot}075T - 9{\cdot}8 \text{ kcal. mole}^{-1}$$

From this $\log_{10} A = 16{\cdot}4$ l.^{2} mole^{-2} min.$^{-1}$ and $E = 9{\cdot}8 + 14Q$ kcal. mole^{-1}.

Since $\boldsymbol{R}T \log_e k_3$ is a constant for the reactions of αα-diphenyl-β-picrylhydrazyl with anilines under a given set of conditions, the nitrogen atom of the aniline seems to acquire a positive charge in the step of the reaction which controls the rate. Braude, Brook, and Linstead [1] who found that rates of reactions of αα-diphenyl-β-picrylhydrazyl with hydroaromatic compounds obeyed a third-order law, concluded that the reaction involves the reversible association of two of the reacting species followed by attack on this intermediate

[16] Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 96: "Physical Organic Chemistry," McGraw-Hill Book Co., New York 1940, Chap. 7.

by a third component. For the aromatic primary amines the transfer of an electron from the amine to the hydrazyl, in the way suggested by Hammond, Sen, and Boozer,[6] seems the most likely mode of association.

$$\text{Hydrazyl} + \text{Ar·NH}_2 \rightleftharpoons [\text{Hydrazine anion}][\text{Ar·NH}_2^+]$$

The aromatic primary amines give a third-order reaction with αα-diphenyl-β-picrylhydrazyl, but other amines give a second-order reaction. The second-order rate constants reported by Hazell and Russell [4] for 20° in benzene and estimated for 77° by extrapolation of their figures are given below:

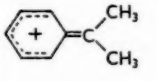
k (l. mole^{-1} min.$^{-1}$)	*N*-Phenyl-β-naphthylamine	*N*-Phenyl-α-naphthylamine	Diphenylamine	Methylaniline
At 20°	35	20	3·2	0·29
At 77°	890	291	139	22

These rates are faster than those shown in Table 3. Hazell and Russell [4] found that αα-diphenyl-β-picrylhydrazine was always a major product in their reactions; that tetraphenylhydrazine was formed in 40% yield from diphenylamine; and that triphenylamine did not react at an appreciable rate with αα-diphenyl-β-picrylhydrazyl. It is therefore likely that αα-diphenyl-β-picrylhydrazyl removes a hydrogen atom off the nitrogen in the diarylamines. The results of other workers [5] support this view, although it has been reported [6] that there was no kinetic isotope effect when *N*-deutero-*N*-methylaniline and -diphenylamine were compared with the undeuterated amines. t-Butylamine gives no appreciable reaction with αα-diphenyl-β-picrylhydrazyl and a hydrogen on the α-carbon atom appears to be necessary in aliphatic amines for reaction (see Table 3).

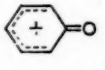
The relative rates [17] (the ratios of the rates for substituted to unsubstituted compound k/k_0) of solvolysis of substituted αα-dimethylbenzyl chlorides in 90% aqueous acetone at 25° are compared below with rates of reaction of the corresponding substituted phenols with αα-diphenyl-β-picrylhydrazyl in carbon tetrachloride at about 20°. The similarity between the figures suggests that the stages which control the rates in the two reactions are very closely related : [15]

	Relative rates k/k_0	
Substituent	Reaction of phenols with αα-diphenyl-β-picrylhydrazyl	Solvolysis of dimethylbenzyl chlorides
p-Methoxy	3300	3360
p-Methyl	13	26
p-t-Butyl	19	14
p-Chloro	0·26	0·31

The stage which controls the rate in the solvolysis of the αα-dimethylbenzyl chlorides almost certainly involves the formation of the carbonium ion (I), and so the stage which controls the rate in the reactions of phenols with αα-diphenyl-β-picrylhydrazyl seems to involve the removal of a hydride ion from the phenolic oxygen atom with the formation of an ion (II) with a positive charge. The second electron may be taken up by one of the nitro-groups of the hydrazyl.



(I)



(II)

The introduction of alkyl groups into phenols brings about a big increase in their efficiency as antioxidants.[18] It is therefore of interest that the substitution of alkyl groups in phenols greatly increases the rate of reaction with αα-diphenyl-β-picrylhydrazyl. The

[17] Brown, Brady, Grayson, and Bonner, *J. Amer. Chem. Soc.*, 1957, **79**, 1897; Brown, Okamoto, and Ham, *ibid.*, p. 1906; Okamoto and Brown, *ibid.*, p. 1909.

[18] Rosenwald, Hoatson, and Chenicek, *Ind. Eng. Chem.*, 1950, **42**, 162; Egloff, Morrell, Lowry, and Dryer, ref. 11.

substitution of any alkyl group in the *para*-position increases the rate about 18 times. Each alkyl group in the *meta*-position increases k about three times, and when there is little if any steric hindrance an alkyl group in an *ortho*-position increases k about eight times. Calculated values of k were obtained by multiplication of 4·2 by these factors. There was fair agreement between the observed and the calculated k values provided one *ortho*-position of the phenol is unsubstituted, so that for such phenols the ratio of calculated to observed value of k is near unity (Table 4, col. 6). When there are alkyl groups in the 2- and the 6-position, the value of k found for the reaction of the phenol with αα-diphenyl-β-picrylhydrazyl is less than the value calculated as described above. The ratio of calculated to observed value of k is about three when 2,6-methyl groups are present. This ratio rises to about 15 when there is a 2-methyl group and a bulky alkyl group in the 6-position, and becomes over a hundred when there are bulky groups in both the 2- and the 6-position. It has been found [19] that the smaller the difference between the OH infrared absorption bands (at about 2·7 μ) in a dilute solution and a concentrated solution or melt, the greater the steric hindrance, and figures [14] are given in col. 7 of Table 4 for differences in these wavelengths.

A direct measure of the oxidation–reduction potential of simple phenols is not possible, but indirect measures of the relative oxidation–reduction potentials of phenols have been made.[20] Penketh's results [13] (col. 4, Table 4) for relative oxidation potentials (E_c) at zero pH are plotted against values of $\log_{10} k$ for the reactions of αα-diphenyl-β-picrylhydrazyl with phenols in Fig. 2. The points for phenols with one or no *ortho*-substituents are marked × and the methoxyphenols have been included. These points fall close to the straight line. If the potentials and k values were derived from closely related reactions, $-RT \log_e k$ would be expected to equal ($23{\cdot}053E_c$ + a constant) kcal. per mole. This relation would give $(23{\cdot}053/2{\cdot}3026)RT$ for the slope of the $\log_{10} k$ against E_c plot and the line in Fig. 2 has been drawn with this slope. The high values of k are only approximate and Penketh claims only an accuracy of ±0·03 v, so that the agreement between the points and the line is as good as could be expected. The points for phenols with two *ortho* groups are marked ⊙ in Fig. 2 and all fall below the line, and the bulkier the groups in the *ortho*-positions the farther below the line do the points fall. Penketh [13] has discussed the relations between his potentials and various other measures of antioxidant activity, so that further discussion here appears to be unnecessary.

The authors thank Dr. H. Clough and Dr. R. W. G. Preston for samples of nineteen of the phenols.

Imperial Chemical Industries Limited,
Research Department, Black Fan Road,
Welwyn Garden City, Herts.

[*Received, February 16th,* 1959.]

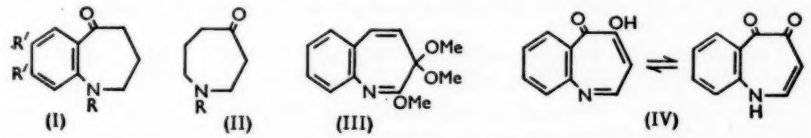
[19] Coggeshall, *J. Amer. Chem. Soc.*, 1947, **69**, 1620.
[20] Conant, *ibid.*, 1926, **48**, 3220; Fieser, *ibid.*, 1930, **52**, 5204.

631. *Azatropolones.*

By A. H. Rees.

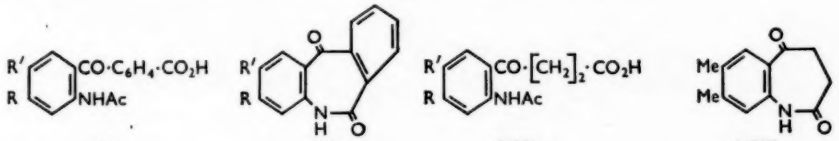
Succinylation * of *N*-acetyl-3 : 4-xylidine and subsequent deacetylation give an amino-acid which can be cyclised to 2 : 3 : 4 : 5-tetrahydro-7 : 8-dimethyl-2 : 5-dioxobenz[*f*]azepine in 30% overall conversion. From this compound a variety of new compounds has been made including two which are formally azatropolones. Evidence has been obtained, however, that these are not heteroaromatic.

Since Dewar [1] postulated the aromatic tropolone system there has been much speculation as to the existence and nature of heterocyclic analogues and in recent years the chemistry of compounds containing a seven-membered nitrogenous ring has expanded appreciably.[2] Ketones such as (I; R = Me and *p*-$C_6H_4Me{\cdot}SO_2$, R′ = H) and (II; R = H and CH_2Ph),



(I) (II) (III) (IV)

though reported,[3] have not yet been used to afford azatropolones. The nearest approach has been 2 : 3 : 3-trimethoxybenz[*f*]azepine [4] (III) but demethylation caused ring contraction to give methyl quinaldate. Although the tropolone-like compound (IV) remains to be synthesised, two related compounds have been obtained in this study. From substituted anilides Kränzlein [5] obtained 2-phthaloyl derivatives (V) which, when boiled with mineral acid gave the amino-acids and thence the lactams (VI). The Friedel–Crafts reaction of anilides with succinic anhydride is now described.



(V) (VI) (VII) (VIII)

It has been reported that *N*-acetyl-*p*-toluidine cannot be acetylated,[6] and attempted succinylation failed, owing perhaps to the opposing effects of the methyl and acetamido-groups. The *meta*-isomer was however converted into its β-carboxypropionyl derivative, which by analogy with the orientation of the phthaloyl-anilide (V; R = Me, R′ = H) and the fact that acetylation of *N*-acetyl-*o*-toluidine occurs *para* to the methyl group,[7] was thought to have structure (VII; R = Me, R′ = H). However, the free amino-acid did not yield a lactam; on deamination it gave β-*o*-toluoylpropionic acid,[8] so it must be 4-β-carboxypropionyl-3-methylacetanilide.

* In this paper, " succinylation " denotes introduction of a $HO_2C{\cdot}CH_2{\cdot}CH_2{\cdot}CO-$ group.

[1] Dewar, *Nature*, 1945, **155**, 50.

[2] Lyle, U.S.P. 2,683,145/1954; Leonard, Fox, and Oki, *J. Amer. Chem. Soc.*, 1954, **76** 5708; Bertho, *Chem. Ber.*, 1957, **90**, 29; Butenandt, Biekert, and Neubert, *Annalen*, 1957, **603**, 200; Lloyd, Matternas, and Horning, *J. Amer. Chem. Soc.*, 1955, **77**, 5932.

[3] (*a*) Astill and Boekelheide, *ibid.*, p. 4079; (*b*) Braunholtz and Mann, *J.*, 1957, 4174; Proctor and Thomson, *ibid.*, p. 2312; Yokoo and Morosawa, *Bull. Chem. Soc. Japan*, 1956, **29**, 631.

[4] Look, *Diss. Abs.*, 1957, **17**, 36.

[5] Kränzlein, *Ber.*, 1937, **70**, 1952.

[6] Mehta, Sacha, and Patel, *J. Indian Chem. Soc.*, 1950, **33**, 867.

[7] Sacha and Patel, *ibid.*, p. 129.

[8] Dauben and Tilles, *J. Org. Chem.*, 1950, **15**, 785.

Since it appeared desirable to block the position *para* to the acetamido-group, *N*-acetyl-3 : 4-xylidine and 2-naphthylamine were next studied and the product (VII; R = R′ = Me) from the former, being formed in better yield, was used for further work. Hydrolysis with acid gave the amine salt and though this did not give a lactam, the free amino-acid could be cyclised thermally with or without a solvent to 2 : 3 : 4 : 5-tetrahydro-7 : 8-dimethyl-2 : 5-dioxobenz[*f*]azepine (VIII) which was characterised as carbonyl derivatives.

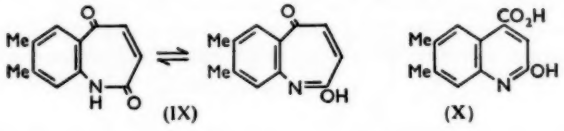
N-Arylsuccinamic acids, prepared for attempts at shortening this synthesis, cyclised, not on to the ring as desired, but back on to the nitrogen atom to give *N*-arylsuccinimides. The latter could not be converted into keto-lactams under the conditions used for rearranging diacetylaniline to *p*-acetylacetanilide.[9]

The ultraviolet spectrum of the keto-lactam (VIII) is tabulated below and the infrared spectrum confirmed the structure (CO band 5·97 μ). The keto-lactam, with selenium dioxide under the conditions for the oxidation of oxindole to isatin,[10] did not yield a definite product. An attempt at protecting the NH group by acetylation gave a compound which still contained one active hydrogen atom and was probably the enol acetate. The acid (VII; R = R′ = Me) could not be cyclised to the *N*-acetyl derivative of the keto-lactam.

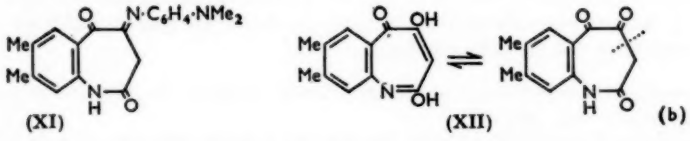
log ε	5·55	4·95	4·90	4·55	4·00	2·40	2·30
$\lambda_{max.}$	235	265		320		430	
$\lambda_{min.}$			255		288 *		410

* Shoulder at 362—370 mμ (log ε 3·65—3·55).

The keto-lactam was then brominated, and a derivative was obtained from which the halogen acid was easily eliminated giving 2 : 5-dihydro-7 : 8-dimethyl-2 : 5-dioxobenz[*f*]-azepine (IX) which was examined briefly. It was stable to dilute mineral acid, in contrast to the keto-lactam whose ring was opened thereby. The infrared spectrum showed no true carbonyl band and a dinitrophenylhydrazone could not be obtained. It was not possible to decide between OH and NH bands in the higher-frequency region though an NH group was indicated by a band at 1660 cm.$^{-1}$. The compound (IX) was not soluble in



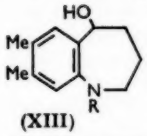
cold dilute aqueous alkali. Hot alcoholic alkali caused a reaction: though this is not yet fully understood, a tropone type of ring contraction [11] did not occur; 2-hydroxy-6 : 7-dimethylquinoline-4-carboxylic acid (X) was not found as a product and it is thought that the seven-membered ring was opened at the 3 : 4-double bond. This double bond could not be introduced into the keto-lactam (VIII) by dehydrogenation which should be easy if the compound (IX) were aromatic.



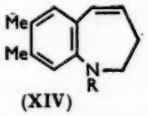
Of greater interest is 2 : 3 : 4 : 5-tetrahydro-7 : 8-dimethyl-2 : 4 : 5-trioxobenz[*f*]-azepine (XII) which was prepared from the keto-lactam (VIII) by condensation with *NN*-dimethyl-*p*-nitrosoaniline followed by acid-hydrolysis of the intermediate anil (XI). The

[9] Chattaway, *J.*, 1904, **85**, 386.
[10] Giovannini and Portmann, *Helv. Chim. Acta*, 1948, **31**, 1396.
[11] Bartels-Keith, Johnson, and Langemann, *J.*, 1952, 4461.

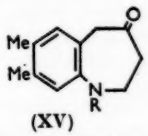
trione (XII) was alkali-soluble but prolonged action gave two products, the acid (X) and 5 : 6-dimethylisatin. It is considered that the common precursor was *N*-acetyl-4 : 5-dimethylisatic acid formed by ring opening of form (XIIb) as indicated. Thus from chemical evidence a heterotropolone behaviour and nature for (XII) is excluded. The infrared spectra of compounds (XI) (as hydrochloride) and (XII) conform to the same type as that of (IX), indicating mainly the existence of tautomerism.



(XIII)



(XIV)



(XV)

In a compound such as (IV), lactam–lactim tautomerism would be impossible, except perhaps by the vinylogous system, NH·CH:CH·CO $\rightleftharpoons$ N:CH·CH:C(OH). In preliminary attempts to prepare starting material, reduction of the keto-lactam (VIII) by lithium aluminium hydride gave the hydroxy-amine (XIII; R = H). Acetylation [12] and oxidation [13] then gave 1-acetyl-2 : 3 : 4 : 5-tetrahydro-7 : 8-dimethyl-5-oxobenz[*f*]azepine (I; R = Ac, R′ = Me) and thence the free amino-ketone. Attempts at preparing the isomeric 4-ketone (XV) failed. Dehydration [3a] of the hydroxy-amine (XIII; R = H) gave 2 : 3-dihydro-7 : 8-dimethylbenz[*f*]azepine (XIV; R = H). After acetylation, the 4 : 5-double bond was oxidised with perbenzoic acid but a polymer resulted. Addition of bromine to the double bond gave a dibromide, but with silver acetate this afforded an undistillable oil which when hydrolysed [14] gave only traces of ketone.

Experimental

Succinylation of N-*Acetyl*-m-*toluidine*.—By reaction as in the succinylation of acetanilide,[15] 4-β-*carboxypropionyl*-3-*methylacetanilide*, m. p. 192° (from alcohol), was obtained in 47% yield with 39% recovery (Found: C, 62·6; H, 6·1; N, 5·3. $C_{13}H_{15}O_4N$ requires C, 62·6; H, 6·1; N, 5·6%).

Acetyl-*p*-toluidine was not acylated under these conditions or after 12 hr. in nitrobenzene at 140°.

4-β-*Carboxypropionyl*-3-*methylaniline*.—Its *N*-acetyl derivative (above; 16·5 g.) was heated for 3 hr. on a steam-bath with 40% sodium hydroxide solution (20 ml.), then left to cool. Adding 6N-hydrochloric acid to pH 6 precipitated the *amino-acid* (12·9 g.), m. p. 158° (from aqueous alcohol) (Found: C, 64·05; H, 6·4; N, 7·1. $C_{11}H_{13}O_3N$ requires C, 63·75; H, 6·3; N, 6·8%).

The base (6·6 g.) gave, by Kornblum and Iffland's method,[16] β-*o*-toluoylpropionic acid (5·7 g.), m. p. 101° (from light petroleum), identical with a sample kindly provided by Professor Dauben [8] (Found: C, 68·9; H, 6·3. Calc. for $C_{11}H_{12}O_3$: C, 68·7; H, 6·3%).

Succinylation of N-*Acetyl*-3 : 4-*xylidine*.—The powdered amide (32·6 g.) was added to a suspension of succinic anhydride (30 g.) in carbon disulphide (350 ml.). Powdered aluminium chloride (200 g.) was then added with stirring. After the initial reaction had subsided the mixture was refluxed until a dark red complex was formed. The supernatant liquor was decanted and the residue decomposed with ice, dilute hydrochloric acid, and wet benzene. Filtration left 2-β-*carboxypropionyl*-4 : 5-*dimethylacetanilide* (VII; R = R′ = Me) which was triturated with benzene, then water, and dried [yield, 50%, 26·4 g.; m. p. 179° (from aqueous alcohol) (Found: C, 64·2; H, 6·7; N, 5·1. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5; N, 5·3%). From the benzene liquors, the starting amide (40%) was recovered.

Succinylation of N-*Acetyl*-2-*naphthylamine*.—By the above method the 1-β-*carboxypropionyl derivative* was obtained in poor yield, with m. p. 229° (from alcohol) (Found: C, 67·05; H, 5·35; N, 4·8. $C_{16}H_{15}O_4N$ requires C, 67·35; H, 5·3; N, 4·9%).

[12] Synge, *Biochem. J.*, 1939, **33**, 1290.
[13] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[14] Newhall, Harris, Holly, Johnston, Richter, Walton, Wilson, and Folkers, *ibid.*, 1955, **77**, 5646.
[15] English, Clapp, Cole, and Krapcho, *ibid.*, 1945, **67**, 2263.
[16] Kornblum and Iffland, *ibid.*, 1949, **71**, 2141.

XUM

2-β-*Carboxypropionyl*-4 : 5-*dimethylaniline*.—The crude acetyl derivative (VII; R = R′ = Me) (28·7 g.) was refluxed for 3 hr. with 6N-hydrochloric acid (110 ml.). Charcoal (0·5 g.) was added and after filtration the *hydrochloride monohydrate* (20·2 g.), m. p. 172° (from dilute hydrochloric acid), separated (Found: C, 52·1; H, 6·55; N, 5·1; Cl^-, 12·7. $C_{12}H_{15}O_3N,HCl,H_2O$ requires C, 52·3; H, 6·6; N, 5·1; Cl^-, 12·9%). The salt (17·7 g.) was ground in a mortar with addition of N-sodium hydroxide until the pH rose to 7—8. After being collected and washed with water the free *amino-acid* (13·7 g.), m. p. 137° (from aqueous alcohol), was left (Found: C, 65·0; H, 6·85; N, 6·4. $C_{12}H_{15}O_3N$ requires C, 65·1; H, 6·83; N, 6·3%).

Cyclisation of the Amino-acid.—The amino-acid was heated in a vacuum at about 180°/0·1 mm. pressure; the keto-lactam (VIII) was obtained as a white sublimate, m. p. 199° (from tetrahydrofuran).

Alternatively the amino-acid (16·2 g.) was refluxed for 6½ min. in tetralin (55 ml.). On cooling, the *keto-lactam* crystallised (13 g.) (Found: C, 70·8; H, 6·7; N, 6·8. $C_{12}H_{13}O_2N$ requires C, 70·9 H, 6·45; N, 6·9%). The red *dinitrophenylhydrazone* had m. p. 300° (decomp.) (from acetic acid) (Found: C, 56·2; H, 4·5; N, 18·2. $C_{18}H_{17}O_5N_5$ requires C, 56·2; H, 4·5; N, 18·3%). The *oxime* prepared under neutral conditions had m. p. 226° (from alcohol) (Found: C, 65·6; H, 6·4; N, 13·1. $C_{12}H_{14}O_2N_2$ requires C, 66·0; H, 6·5; N, 12·8%). The infrared spectrum of the keto-lactam (in Nujol) had peaks at 3220w, 3110w, 2960s, 1675s, 1615m, 1575w, 1495m, 1460m, 1445m, 1415s, 1385w, 1370w, 1330w, 1305w, 1265w, 1245w, 1215w, 1180w, 1150w, 1025w, 995w, 965w, 925w, 905w, 875w, 820w, and 740w $cm.^{-1}$.

Preparation of N-*Arylsuccinamic Acids*.—Solutions of the aniline and succinic anhydride (1 equiv.) in dioxan were mixed and heated for 10 min. on a steam-bath. On cooling, the anilide was deposited. Thus were prepared *N*-phenylsuccinamic acid and its 3-methyl, m. p. 133° (from water), and 3 : 4-*dimethyl derivative*, m. p. 143° (from aqueous alcohol) (Found: C, 65·1; H, 6·8; N, 6·3. $C_{12}H_{15}O_3N$ requires C, 65·15; H, 6·8; N, 6·3%).

Cyclisation of Arylsuccinamic Acids.—Phenylsuccinamic acid (4 g.) and aluminium chloride (7 g.), warmed to 170° in *o*-dichlorobenzene (40 ml.), gave after steam-distillation an aqueous suspension of *N*-phenylsuccinimide (1·5 g.). In absence of a solvent [17] hydrolysis took place. Boron trifluoride–ether complex gave the imide in improved yield.

By use of an excess of boron trifluoride–ether at 125°, *N*-*m*-tolylsuccinamic acid gave *N*-*m*-tolylsuccinimide [18] and some diethyl succinate.

Attempted Rearrangement of N-*Arylsuccinimides*.—The imide (3·5 g.) was heated with anhydrous zinc chloride (1·2 g.) for 20 hr. at 180°. On addition of water and filtration, the imide was recovered. At higher temperatures decomposition began. Rearrangement did not occur on use of boron trifluoride, aluminium chloride in *o*-dichlorobenzene, or molten sodium chloride–aluminium chloride.[19]

Acetylation of the Keto-lactam.—The keto-lactam (3 g.), refluxed for ½ hr. with excess of acetyl chloride, gave on concentration an *acetyl derivative* (1·5 g.), m. p. 212° (from acetic acid) (Found: C, 68·8; H, 6·25; active H; 0·44; N, 5·7. $C_{14}H_{15}O_3N$ requires C, 68·8; H, 6·2; active H, 0·41; N, 5·7%). From the mother-liquor an *isomer* was obtained having m. p. 225° (depressed by the acetyl derivative) (Found: C, 68·9; H, 6·2; active H, 0·49; N, 5·5%).

Bromination of the Keto-lactam.—Chloroform solutions of bromine (0·25 ml.) and the keto-lactam (1 g.) were mixed and when the colour had faded the solution was concentrated at 40°. Benzene was then added and after decantation from some tar the solution was rapidly washed until neutral, dried, and set aside; the yellow *bromo-keto-lactam* deposited had m. p. *ca.* 135° (decomp.) (Found: C, 51·5; H, 4·4; N, 5·05; Br, 28·0. $C_{12}H_{12}O_2NBr$ requires C, 51·1; H, 4·3; N, 5·0; Br, 28·3%).

Dehydrobromination of the Bromo-keto-lactam.—To a chloroform solution of the bromo-compound was added hydrated sodium acetate. On shaking, filtration, and storage, yellow 2 : 5-*dihydro*-7 : 8-*dimethyl*-2 : 5-*dioxobenz*[f]*azepine* (IX), m. p. 258° (from propanol), was deposited (0·55 g.) (Found: C, 71·55; H, 5·9; N, 7·05. $C_{12}H_{11}O_2N$ requires C, 71·6; H, 5·5; N, 6·95%). The compound was not stable in borneol, the molecular weight decreasing.

A dinitrophenylhydrazone, obtained slowly as a red oil from alcohol solution, became tarry and dark and may not have been that of the dione.

The infrared spectrum (in Nujol) had peaks at 3240m, 3170m, 3110m, 2930s, 1665m, 1615s,

[17] Norris and Klemka, *J. Amer. Chem. Soc.*, 1940, **62**, 1432.
[18] Miolati and Longo, *Rend. Accad. Lincei*, 1896, [v], **4**, I, 357.
[19] Bruce, Sorrie, and Thomson, *J.*, 1955, 2403.

1585s, 1490w, 1460s, 1415m, 1375m, 1345w, 1280w, 1265w, 1230m, 1185m, 1150w, 1025w, 990w, 915w, 875m, 800w, 755w, and 745w cm.$^{-1}$.

Action of Alkali on the Dione (IX).—The dione (0·5 g.) in dioxan (5 ml.) was refluxed for ½ hr. with 2N-sodium hydroxide (0·9 ml.) and water (2 ml.). On cooling, dione (0·25 g.) and a black tar were obtained.

To the dione (0·5 g.) in alcohol (60 ml.) was added potassium hydroxide (1 g.) in water (20 ml.). A stable red colour developed. After 24 hr., and 1 hr. on a steam-bath, the solution was evaporated to small bulk and filtered. The residue was suspended in water and acidified; it changed from brown-red to yellow-brown. After collection, washing, and drying it had no m. p. below 400°. The alkaline filtrate when acidified gave a brown solid (0·3 g.), insoluble in sodium hydrogen carbonate solution and soon becoming virtually insoluble in caustic alkali solution. The sticky solid could not be recrystallised and it gave an unstable dinitrophenylhydrazone.

Preparation of 6 : 7-*Dimethyl*-2-*oxoquinoline*-4-*carboxylic Acid* (X).—The method given in *Org. Synth.*[20] gave the acid apparently unaccompanied by the isomer obtained in its original preparation.[21] The higher m. p. recorded for material crystallised from acetic acid has now been shown to be due to the formation of a *monoacetate*, m. p. 360° (Found: C, 60·6; H, 5·6; N, 5·05. $C_{12}H_{11}O_3N,CH_3{\cdot}CO_2H$ requires C, 60·6; H, 5·45; N, 5·0%). The infrared spectrum of the intermediate 1-acetyl-5 : 6-dimethylisatin was taken for reference, peaks (Nujol) being at 3110w, 3050w, 2940s, 2870m, 1760s, 1735s, 1720s, 1620s, 1580m, 1475s, 1455m, 1425w, 1390s, 1325s, 1285m, 1230s, 1195w, 1185w, 1160m, 1105w, 1045w, 1025w, 1015w, 1000w 960w, 905m, 810w, and 805w cm.$^{-1}$.

Condensation of the Keto-lactam with p-*Nitrosodimethylaniline*.—The nitroso-compound (1·5 g.) and the keto-lactam (1 g.) were dissolved in hot methanol, and 2N-alkali (2 ml.) was added. The mixture was set aside and deposited 4-p-*dimethylaminophenylimino*-2 : 3 : 4 : 5-*tetrahydro*-6 : 7-*dimethyl*-2 : 5-*dioxobenz*[f]*azepine* (XI), m. p. 316° (from dimethylformamide) (Found: C, 71·5; H, 6·35; N, 12·3. $C_{20}H_{21}O_2N_3$ requires C, 71·6; H, 6·3; N, 12·5%). The red anil gave a yellow-green hydrochloride which regenerated the base with alkali. The salt was not easily purified as the anil was hydrolysed by acid, but a sample had m. p. 265° (in block at 250°) (Found: N : Cl, 1·19. $C_{20}H_{22}O_2N_3Cl$ requires N : Cl, 1·20), $\nu_{max.}$ (in Nujol) 3300s, 2940s, 2520w, 2450w, 1650s, 1625s, 1590s, 1560m, 1515m, 1485s, 1445m, 1375m, 1345w, 1320w, 1305w, 1230w, 1180m, 1140m, 1115w, 965w, 890w, 855w, 840w, 810w, 790w, 755w, and 740w cm.$^{-1}$.

Acid Hydrolysis of the Anil (XI).—The anil (1·2 g.) was refluxed for ½ hr. with concentrated hydrochloric acid (10 ml.), a dark suspension being obtained. The solid was collected and washed with water, hot alcohol, benzene, and acetone,[22] then dried, giving 2 : 3 : 4 : 5-*tetrahydro*-7 : 8-*dimethyl*-2 : 4 : 5-*trioxobenz*[f]*azepine* (XII) (0·5 g.), yellow-green, m. p. 290° (decomp.) (Found: C, 66·1; H, 5·05; N, 6·5. $C_{12}H_{11}O_3N$ requires C, 66·35; H, 5·1; N, 6·45%), $\nu_{max.}$ (in Nujol) 3280m, 3120w, 2940s, 1660s, 1620m, 1590s, 1570s, 1485w, 1460s, 1430m; 1375m, 1360m, 1340m, 1260w, 1255w, 1225m, 1185m, 1140s, 1015w, 955w, 890w, 875w, 855w, 800w, 755w, and 740w cm.$^{-1}$.

Action of Alkali on the Trione (XII).—The trione (0·25 g.) in 2N-sodium hydroxide was heated for ¾ hr. on a steam-bath. On acidification an acid was precipitated which, recrystallised from acetic acid, had m. p. 360° alone or mixed with the acetate of the acid (X). The aqueous mother-liquor slowly gave a mixture of a buff-coloured with a red solid. Addition of sodium hydrogen carbonate to pH 8 left only the red solid (5 : 6-dimethylisatin), as needles, m. p. 210°, raised to 212° (m. p. and mixed m. p.) by crystallisation from benzene.

Reduction of Keto-lactam (VIII) *by Lithium Aluminium Hydride*.—To the hydride (7 g.) in tetrahydrofuran (100 ml.) was added rapidly a solution of the keto-lactam (10 g.) in the same solvent (200 ml.). After 2 days' stirring with refluxing, ethyl acetate (10 ml.) and water (25 ml.) were added dropwise. Filtration and evaporation gave a base (6·6 g.) which solidified. A portion, rapidly distilled at low pressure from a retort, then recrystallised from methanol, had m. p. 127° or 132—135° (bath pre-heated to 120°). This was 2 : 3 : 4 : 5-*tetrahydro*-5-*hydroxy*-7 : 8-*dimethylbenz*[f]*azepine* (XIII; R = H) (Found: C, 75·05; H, 8·6; N, 7·25. $C_{12}H_{17}ON$

[20] Marvel and Hiers, in *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 327; Jacobs, Winstein, Linden, Robson, Levy, and Seymour, *Org. Synth.*, Coll. Vol. III, 1955, p. 456.
[21] King and Wright, *Proc. Roy. Soc.*, 1948, *B*, **135**, 271.
[22] Ityerrah and Mann, *J.*, 1958, 467.

XUM

requires C, 75·35; H, 8·95; N, 7·3%). Solvent extraction of the alumina gave more of the hydroxy-amine (3 g.). Use of acid or alkali in the work-up caused dehydration to 2 : 3-*dihydro*-7 : 8-*dimethylbenz*[f]*azepine* (XIV; R = H), m. p. 89° (from alcohol) (Found: C, 83·3; H, 8·7; N, 7·8. $C_{12}H_{15}N$ requires C, 83·2; H, 8·7; N, 8·1%). Both bases gave the same *picrate*, m. p. 174° (decomp.) (from alcohol) (Found: N, 13·7. $C_{18}H_{18}O_7N_4$ requires N, 13·9%). The unsaturated base was the stronger and reduced alcoholic silver nitrate. Both bases, with acetic acid–anhydride, gave 1-*acetyl*-2 : 3-*dihydro*-7 : 8-*dimethylbenz*[f]*azepine* (XIV; R = Ac), m. p. 95° (from ether) (Found: C, 77·8; H, 7·95; N, 6·5. $C_{14}H_{17}ON$ requires C, 78·1; H, 8·0; N, 6·5%).

Preparation and Oxidation of 1-*Acetyl*-2 : 3 : 4 : 5-*tetrahydro*-5-*hydroxy*-7 : 8-*dimethylbenz*[f]-*azepine* (XIII; R = Ac).—To the hydroxy-amine (XIV; R = H) (0·96 g.) were added 2N-sodium hydroxide (5 ml.) and acetic anhydride (1 ml.), dropwise at $<5°$. The mixture was shaken in an ice-bath for several hours, then extracted with benzene, giving on evaporation of the extract a neutral solid (1 g.) which could not be satisfactorily purified; a sample triturated with methanol had m. p. 136°, depressed on admixture with the hydroxy-amine.

Chromic oxide (1·3 g.) in pure pyridine (15 ml.) was mixed with the crude *acetyl compound* (1 g.) in pyridine (8 ml.) and left overnight. Then water was added and the mixture extracted with 1 : 1 ether–benzene (3 × 33 ml.). Evaporation of the dried extracts left a solid (0·7 g.). Crystallisation from methanol gave 2 : 3 : 4 : 5-*tetrahydro*-7 : 8-*dimethyl*-5-*oxobenz*[f]*azepine* (I; R = H, R′ = Me), m. p. 106° (Found: C, 76·35; H, 7·9; N, 7·4. $C_{12}H_{15}ON$ requires C, 76·15; H, 8·0; N, 7·4%). This ketone was acid-soluble and gave a very poor yield of a dinitrophenylhydrazone, m. p. 205°, probably as a rather soluble hydrochloride.

The ketone mother-liquor, when worked up, gave the N-*acetyl-ketone* (I; R = Ac, R′ = Me), m. p. 105° (Found: C, 72·5; H, 7·1; N, 6·2. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·4; N, 6·05%). Its dinitrophenylhydrazone was very soluble and deacetylation was suspected. The *semi-carbazone*, obtained from alcohol, had m. p. 206° (Found: N, 19·3. $C_{15}H_{20}O_2N_4$ requires N, 19·4%).

1-*Acetyl*-4 : 5-*dibromo*-2 : 3 : 4 : 5-*tetrahydro*-7 : 8-*dimethylbenz*[f]*azepine*.—To the unsaturated amide (XIV; R = Ac) (1 g.) in chloroform was added bromine (0·24 ml.). Evaporation of the rapidly decolorised solution left the *dibromo-compound*, m. p. 173° (from methanol) (Found: C, 45·1; H, 4·5; N, 3·9; Br, 44·0. $C_{14}H_{17}ONBr_2$ requires C, 44·8; H, 4·7; N, 3·7; Br, 43·0%).

The author acknowledges the benefit of discussions with Professors F. Bergel and C. W. L. Bevan and thanks Dr. D. H. Irvine for the ultraviolet spectrum and Messrs. Roche Products Ltd. for gifts of xylidine and Dr. A. A. Wagland for infrared spectra.

UNIVERSITY COLLEGE, IBADAN, NIGERIA. [*Received, February 27th*, 1959.]

---

632. *Nitrosation, Diazotisation, and Deamination. Part VII.* The Reactivities of Some Aromatic Amines towards Dinitrogen Trioxide.*

By L. F. LARKWORTHY.

The rates of diazotisation in dilute perchloric acid of *p*-chloroaniline, *p*-aminophenyltrimethylammonium perchlorate, and *p*-methoxyaniline have been investigated. Dinitrogen trioxide has been shown to be the most important nitrosation carrier in their diazotisation. With *p*-amino-phenyltrimethylammonium perchlorate acid-catalysis had to be suppressed to obtain a pure reaction with dinitrogen trioxide.

Rate constants, calculated upon the assumption that the molecular amine is the reactant, have been shown to obey the Hammett equation.

PREVIOUS papers in this Series elucidated the range of nitrosation mechanisms that give rise to diazotisation in dilute perchloric acid. It was shown that with a given amine the mechanism depended to a large extent on the acidity and the reactant concentration. The work described in the present paper is part of that being carried out to investigate how the nature of the amine influences the mechanism of nitrosation, with particular

* Part VI, *J.*, 1958, 88.

reference to the reactivity of different amines towards dinitrogen trioxide. For that purpose the kinetics of the diazotisation of three contrasting amines, *p*-chloroaniline, *p*-aminophenyltrimethylammonium perchlorate, and *p*-methoxyaniline, have been studied in detail.

An account of the diazotisation of aniline in an excess of perchloric acid has been given in Part II.[1] The overall kinetic order falls from 3 to 2 as the excess of acid is reduced because the order with respect to aniline falls from 1 to 0. The limiting kinetic equations for the reaction are:

$$\text{Rate} = k_3''[\text{Ar}\cdot\text{NH}_2][\text{HNO}_2]^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$\text{Rate} = k_2''[\text{HNO}_2]^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

As shown in Part I [2] the existence of the two equations demonstrates that the nitrosation carrier is dinitrogen trioxide. The bracketed quantities are molecular rather than stoicheiometric, and the rate constants are molecular constants, *i.e.*, they are calculated from the concentrations of molecular amine and undissociated nitrous acid. Stoicheiometric constants are those calculated from the total concentrations of the ionised and un-ionised forms of the amine and the nitrous acid. The use of these rate constants is discussed in detail in Part I. Stoicheiometric constants are denoted by a superposed bar. The number of primes indicates the order in nitrous acid of the rate equation to which the stoicheiometric or molecular rate constant belongs.

Even in the most simplified system, that containing an excess of perchloric acid, several nitrosation carriers can exist,[2] *e.g.*, NO^+, $NO\cdot OH_2^+$, $NO\cdot NO_2$, NO·OH. Thus, before the reactivities of different amines towards dinitrogen trioxide can be compared, it is necessary to chose experimental conditions in which diazotisation by carriers other than dinitrogen trioxide is negligible. How this is done will be made clear in the text. Then rate constants, obtained in conditions where equation (1) holds, can be used for the comparison of reactivities.

(1) *The Diazotisation of* p-*Chloroaniline.*—Values of the overall kinetic order, determined by the half-life method, are given in Table 1.

TABLE 1. *Diazotisation of* p-*chloroaniline: overall kinetic order in various concentrations of perchloric acid in excess.*

Free $[H^+]$	1·05	0·52	0·051	0·0049
Order	3·0	3·0	2·9	2·2

(a) *Second-order region.* The second-order reaction in the diazotisation of aniline has been found to obey equation (2) rather than equation (3) which was assumed by earlier workers without any evidence of the reactant orders:

$$\text{Rate} = k_2'[\text{Ar}\cdot\text{NH}_2][\text{HNO}_2] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

That *p*-chloroaniline is diazotised according to the same second-order equation as aniline is shown by the behaviour of the rate constants $\bar{k}_2''$ and $\bar{k}_2'$ in a run (Table 5) in which unequal concentrations of amine and nitrous acid were used. This has been confirmed by showing that doubling the amine concentration hardly affected the rate (Figure; runs 19 and 20).

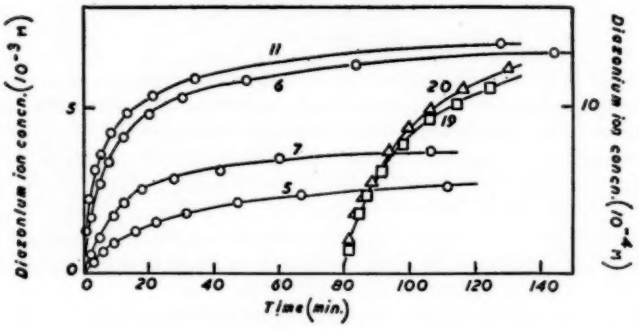
When the reaction is no longer amine-dependent the rate-controlling process is the formation of the dinitrogen trioxide for which $\bar{k}_2''$ in Table 5 is the stoicheiometric second-order rate constant. The molecular rate constant calculated from the mean value of $\bar{k}_2''$, by using $4{\cdot}5 \times 10^{-4}$ mole $l.^{-1}$ for the acidity constant of nitrous acid, is 0·69 $sec.^{-1}$ $mole^{-1}$ l. This compares reasonably well with the value of 0·85 $sec.^{-1}$ $mole^{-1}$ l. found previously [1] because there was some slight amine-dependence in the excess of acid used in this run.

[1] Part II, Hughes, Ingold, and Ridd, *J.*, 1958, 65.
[2] Part I, *idem*, *J.*, 1958, 58.

XUM

(b) *Third-order region.* The Figure shows how doubling the amine concentration (runs 5 and 7) doubled the initial rate, whereas doubling the nitrous acid concentration (runs 6 and 7) quadrupled the initial rate. Doubling the perchloric acid concentration approximately halved the initial rate (runs 6 and 11) because it halved the free amine concentration. These results show that the kinetic equation (1) is operating.

The effect of reactant concentrations on initial rates in the diazotisation of p-*chloroaniline at* 0°. *The right-hand scale applies to runs* 19 *and* 20 *whose time zero is* 80.



Initial stoicheiometric concentrations.

Run	Amine	$[HNO_2]$	$[H^+]$	Run	Amine	$[HNO_2]$	$[H^+]$
5	0·00400	0·00400	1·05	11	0·00795	0·00795	0·525
7	0·00796	0·00398	1·05	19	0·00164	0·00164	0·0049
6	0·00797	0·00797	1·05	20	0·00328	0·00164	0·0049

Table 2 illustrates in detail the acid-dependence of the third-order stoicheiometric and molecular rate constants.

TABLE 2. *Diazotisation of* p-*chloroaniline: acid-dependence of the third-order stoicheiometric* ($\bar{k}_3'$) *and molecular* (k_3'') *rate constants* (*sec.*$^{-1}$ *mole*$^{-2}$ *l.*^{2}).

Acidity constant of $HNO_2 = 4{\cdot}5 \times 10^{-4}$ mole l.$^{-1}$.
Acidity constant of amine cation $= 1{\cdot}55 \times 10^{-4}$ mole l.$^{-1}$.

Run	$[H^+]$	Amine as base (%)	Un-ionised nitrous acid (%)	$\bar{k}_3''$	$10^{-4}k_3''$
6	1·05	0·015	100	33·7	22·5
11	0·52	0·03	100	51·5	17·2
14	0·051	0·30	99	272	9·16

The comparatively small increase in rate with hydrogen-ion concentration may be a salt effect. It is certain that there is nothing like first-order dependence on hydrogen-ion concentration, and that the ion $HN_2O_3^+$, claimed by Okano and Ogata [3] as a main agent in the diazotisation of aniline in much weaker acid, cannot be important here.

The observations that rate equations (1) and (2) both hold, and that when the excess of acid is reduced equation (1) gives way to equation (2), prove that the nitrosation carrier is dinitrogen trioxide. Therefore, the third-order rate constants given in Table 2 are measures of the reactivity of the amine towards dinitrogen trioxide.

(2) *The Diazotisation of* p-*Aminophenyltrimethylammonium Perchlorate.*—The overall reaction order was found to be 2·2 in 0·0051M-acid, and 2·5 in 0·129M-acid. Some runs have been carried out in more concentrated acid. These did not give the third-order kinetics expected for diazotisation by dinitrogen trioxide, and showed considerable acid-catalysis, both phenomena being probably due to some incursion of diazotisation by the

[3] Okano and Ogata, *J. Amer. Chem. Soc.*, 1953, **75**, 5175.

nitrous acidium ion, which obeys equation (4) and therefore gives second-order kinetics in a constant excess of perchloric acid.[4]

$$\text{Rate} = k_3'[\text{Ar}\cdot\text{NH}_2][\text{HNO}_2][\text{H}^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Diazotisation by dinitrogen trioxide has been favoured by using high nitrous acid concentrations, and, to ensure that the attack of the dinitrogen trioxide on the amine was rate-determining, the free amine concentration has been kept low by using moderate acid and low amine concentrations. Table 7 records first-order stoicheiometric rate constants for two runs, one with an excess of nitrous acid twice that of the other, the rate constants being $0{\cdot}77 \times 10^{-3}$ and $2{\cdot}7 \times 10^{-3}$ sec.$^{-1}$, respectively. Therefore, under these conditions, the reaction is closely of the second order with respect to the nitrous acid. Equation (1) is again the complete rate equation. The mean value of the third-order stoicheiometric rate constant is $3{\cdot}5 \times 10^2$ sec.$^{-1}$ mole^{-2} l.^{2}. If the acidity constant of the amine is taken to be $3{\cdot}09 \times 10^{-3}$ mole l.$^{-1}$ the third-order molecular rate constant is found to be $1{\cdot}4 \times 10^4$ sec.$^{-1}$ mole^{-2} l.^{2}. This is a measure of the reactivity of the amine towards dinitrogen trioxide.

The proof of the validity of equation (1) shows that dinitrogen trioxide can play the dominating part in the diazotisation of this amine provided high enough nitrous acid concentrations are used. With such nitrous acid concentrations the third-order equation should give way to equation (2) as the excess of acid is reduced. This was happening when the order fell from 2·5 to 2·2 as the acid concentration was reduced from 0·129M to 0·0051M, although without detailed examination it is not possible to say how much of the second-order rate was due to the nitrous acidium ion.

Reilly and Drumm [5] have reported that the three amines, p-$\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot[\text{CH}_2]_n\cdot\text{NMe}_3^+$ ($n = 0$, 1, 2), are diazotised at the same second-order rate in 0·002M-hydrochloric acid. They claimed that the rates were equal because the amine cations were the reactants and sufficient acid was present to protonate the amines completely. From the now known value for the acidity constant of the amine with $n = 0$, it can be calculated that this is not so, and it seems likely that the main reaction they were studying was the formation of dinitrogen trioxide according to equation (2). It is likely, too, that catalysis by chloride ion markedly affected their results.

(3) *The Diazotisation of* p-*Methoxyaniline.*—Aniline (pK_a 4·58) is only a little less basic than p-methoxyaniline (pK_a 5·29), and so p-methoxyaniline would be expected to react similarly to aniline. A brief investigation, sufficient to show that this amine is diazotised by reaction with dinitrogen trioxide, has been carried out.

The total reaction order was found to be 3, and the stoicheiometric third-order rate constant $1{\cdot}57 \times 10^2$ sec.$^{-1}$ mole^{-2} l.^{2}, in 0·0175M-perchloric acid. In this acid the percentages of undissociated nitrous acid and molecular amine were 97·4 and 0·029 respectively; these gave a value of $5{\cdot}56 \times 10^5$ sec.$^{-1}$ mole^{-2} l.^{2} for the molecular third-order rate constant.

TABLE 3. *Diazotisation of* p-*methoxyaniline: stoicheiometric and molecular second-order rate constants* (sec.$^{-1}$ mole^{-1} l.).

$[\text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2] = 0{\cdot}01\text{M}$. $[\text{H}^+] = 0{\cdot}002\text{M}$.

Run	$[\text{HNO}_2]$	$\bar{k}_2''$	k_2''
5	0·00025	0·597	0·895
4	0·0001	0·613	0·919

That the order in nitrous acid is two was confirmed by carrying out two runs with a large excess of amine in 0·002M-perchloric acid. The second-order plots were straight lines, and the values for the stoicheiometric and the molecular rate constants are given in

[4] Part IV, Hughes, Ingold, and Ridd, *J.*, 1958, 77.
[5] Reilly and Drumm, *J.*, 1935, 871.

XUM

Table 3. Low nitrous acid concentrations were used in order to emphasise any acid-catalysed component of the reaction. Even so, the reaction was of the second order in nitrous acid, and not of the first order as has been found for the acid-catalysed mechanism. The presence of a very small acid-catalysed component is shown by the slight increase in the value of the second-order rate constant as the nitrous acid concentration is reduced. In an excess of acid as small as 0·002M, the rate-controlling step is expected to be the formation of the dinitrogen trioxide. The molecular rate constant for this has been found[1] to be 0·85 sec.$^{-1}$ mole.$^{-1}$ l. The molecular rate constants in Table 3 are very close to this; hence the same process is rate-controlling here. The slightly high values are due to the acid-catalysis.

(4) *Application of the Hammett Equation.*—If the attack of an amine on dinitrogen trioxide is a bimolecular nucleophilic substitution S_N2, it should be favoured by a high electron density on the nitrogen atom of the amino-group; and there should be a correlation between the basicity of the amine and its rate of reaction with dinitrogen trioxide.

$$XAr{\cdot}NH_2 + NO{\cdot}NO_2 \xrightarrow{\text{Slow}} XAr{\cdot}NH_2{\cdot}NO^+ + NO_2^-$$

$$XAr{\cdot}NH_2{\cdot}NO^+ \xrightarrow[\text{fast steps}]{\text{Several}} XAr{\cdot}N_2^+ + H_2O$$

The results with *p*-chloroaniline, *p*-aminophenyltrimethylammonium perchlorate, *p*-methoxyaniline, and aniline have been correlated by means of the Hammett equation,[6] $\log k/k^0 = \rho\sigma$, where k^0 is the rate constant for the unsubstituted member of a reaction series, k is the rate constant for any member of the series, and ρ and σ have their usual meanings.

Third-order rate constants for the diazotisation of the amines investigated are given in Table 4. These are effectively rate constants for reaction with dinitrogen trioxide.

TABLE 4. *Third-order stoicheiometric* ($\bar{k}_3''$) *and molecular* (k_3'') *rate constants for the diazotisation of some aromatic amines together with their sigma constants.*

Amine	Source	(H^+)	$10^{-3}\bar{k}_3''$	$10^{-5}k_3''$	$\log k_3''$	σ
p-OMe	p. 3119	0·0175	1·57	5·56	5·75	−0·268[a]
Aniline	Part II	0·05	1·62	3·11	5·49	0
p-Cl	Table 2	0·051	2·72	0·916	4·96	0·227[a]
p-NMe_3^+	p. 3119	0·12	3·5	0·14	4·15	0·82[a]

[a] McDaniel and Brown, *J. Org. Chem.*, 1958, **23**, 420.

From the slope of the straight line obtained when the logarithms of the molecular rate constants are plotted against σ, the reaction constant ρ can be calculated to be −1·6. The negative value implies that the reaction is favoured by a high electron density at the reaction centre.[6] Since the amino-nitrogen atom is the reaction centre in diazotisation the electron density on this atom must be a crucial factor. This can only mean that the molecular, basic amine interacts with the nitrosating agent in a bimolecular nucleophilic substitution. Were the conjugate acid of the amine the reactant, the positive pole would obscure, and probably make undectectable, reactivity changes due to substituents *para* to the reaction centre.

From Table 4 it can be seen that the reactivities of amines towards dinitrogen trioxide decrease rapidly as σ becomes more positive, *i.e.*, as the basicities of the amines decrease. Eventually, a stage must be reached when an amine is too weakly basic to react readily with dinitrogen trioxide. Then reaction with a more electrophilic nitrosation carrier must supersede that with dinitrogen trioxide if diazotisation is to occur. Acid-catalysis was important in the diazotisation of *p*-aminophenyltrimethylammonium perchlorate, and of *o*-chloroaniline,[4] and in the latter case was found to be due to reaction with the more

[6] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, 1940, Chap. VII.

electrophilic nitrous acidium ion $NO{\cdot}OH_2^+$. Extrapolation of the results in Table 4 shows that *p*-nitroaniline, with a σ constant of −1·27,[6] is about ten times less reactive than *p*-aminophenyltrimethylammonium perchlorate towards dinitrogen trioxide. This is a sufficient reduction in reactivity, as is reported in the following paper, for *p*-nitroaniline, in similar conditions, to react mainly with the nitrous acidium ion.

Experimental

Kinetic Method, and Preparation of Solutions.—All the runs were carried out at 0°. The rates of diazotisation have been followed by estimating the diazonium ion produced colorimetrically, as described in Part I.[2]

p-Chloroaniline and *p*-methoxyaniline were purified by conventional methods. Standard solutions were made up by dissolving these amines in water to which was added a slight excess of perchloric acid over that required to convert the amines into their perchlorates. The acid helped to dissolve the amines. It was allowed for in the calculation of the excess of perchloric acid used in the runs. *p*-Aminophenyltrimethylammonium chloride hydrochloride, prepared according to the method of Pinnow and Koch,[7] formed colourless plates, m. p. 219° (decomp.) (Found: Cl, 31·6. Calc. for $C_9H_{16}N_2Cl_2$: Cl, 31·8%). This chloride had to be converted into the perchlorate before use, to avoid catalysis by the chloride ions. This was done in solution: the perchlorate was not isolated. A known weight of the chloride was dissolved in water and stirred with an excess of silver oxide for 30 min. The oxide became grey as a coating of silver chloride formed. The chloride and the oxide were filtered off and washed rapidly with water: slow washing caused peptisation of the silver chloride. The solution of the quaternary hydroxide was transferred quantitatively to a volumetric flask, an equivalent amount of perchloric acid added, and the volume made up with water. There was no precipitate with silver nitrate (all the chloride had been removed).

To test whether there had been quantitative conversion into the perchlorate, samples A and B, of identical weights, of the chloride were taken, and B alone was converted into the perchlorate in solution. Sample A was just dissolved in water, the final volumes of the two solutions being the same. Identical solutions of A and B in 0·2M-perchloric acid were then made up, cooled to 0°, and diazotised in nitrous acid in sufficient excess to make the reaction go rapidly to completion. Equal samples were then withdrawn, coupled, and estimated colorimetrically:

		Spekker readings
A, solution	0·0567M	0·293 falling to 0·286 after 12 hr.
B, solution	0·0567M	0·284 ,, 0·276 ,, 12 hr.

The smallness of the fall in the readings during 12 hr. showed that the diazonium ion was stable. Therefore it can be assumed that the readings are proportional to the initial amine concentrations. The readings show that about 3—4% loss of amine had occurred. Similar results were obtained with other solutions and were allowed for in the calculation of the amine concentrations in the runs.

Conditions of Coupling.—In the previous work 2 or 5 ml. samples of the reaction mixture, containing $\geqslant$0·05M-perchloric acid, were run into 27 ml. of the coupling solution consisting of R-salt (0·01M) and borax (0·025M or 0·05M) in water. There was thus no difficulty in the neutralisation of the perchloric acid. The present work has been done in perchloric acid from 0·002M to about 2M. Samples containing dilute acid were neutralised and coupled in the same way as before. Those containing more concentrated acid were neutralised in coupling solutions containing a quantity of borax calculated to ensure that the ratio borax : boric acid after neutralisation of the acid was constant from run to run and not far different from unity. Then the final pH was constant and about 8·5, a value at which coupling takes place readily. Runs in acid more concentrated than 2—3M are not possible by this method because a saturated borax solution is little more than 0·15M. The absorption of the dyes produced by the coupling of the diazonium ions varied a little with the coupling conditions, and whenever the excess of acid was varied drastically the calibration of the Hilger Spekker photo-electric absorptiometer, used to

[7] Pinnow and Koch, *Ber.*, 1897, **30**, 2861.

XUM

estimate the colour densities, was checked. The calibration was made as described in Part I.[2] The calibration curves were approximately linear.

Kinetic Results.—Tables 5—7 contain representative examples of the kinetic results.

TABLE 5. *Diazotisation of* p*-chloroaniline at* 0°*: stoicheiometric second-order rate constants (sec.*$^{-1}$ *mole*$^{-1}$ *l.) calculated according to equations* (2) *and* (3).

Run 20

Stoicheiometric initial concentrations:

$[Ar{\cdot}NH_3^+] = 0{\cdot}00328$, $[HNO_2] = 0{\cdot}00164$, $[H^+] = 0{\cdot}0049$M.

t (min.)	Reaction (%)	$\bar{k}_2''$ (eqn. 2)	$\bar{k}_2'$ (eqn. 3)	t (min.)	Reaction (%)	$\bar{k}_2''$ (eqn. 2)	$\bar{k}_2'$ (eqn. 3)
0	9·2	—	—	18·0	52·7	0·570	0·222
2·45	19·7	0·599	0·275	25·1	60·0	0·565	0·206
5·15	28·5	0·588	0·263	35·5	68·3	0·588	0·195
7·42	34·1	0·570	0·248	49·0	74·7	0·593	0·178
12·5	44·6	0·575	0·236	65·9	78·7	0·557	0·154

Mean value of $\bar{k}_2'' = 0{\cdot}578$.

TABLE 6. *Diazotisation of* p*-chloroaniline at* 0°*: stoicheiometric third-order rate constants in* 0·52M- *and* 0·051M*-acid.*

Run 11

[Reactants] = 0·00795M, $[H^+] = 0{\cdot}52$M.

t (min.)	Reaction (%)	$\bar{k}_3''$ (sec.$^{-1}$ mole^{-2} l.^{2})
0	16·4	—
1·33	28·3	49·3
3·28	39·0	50·5
5·00	45·4	51·2
7·90	53·0	51·7
12·5	60·8	52·6
20·7	67·7	51·6
33·5	74·2	53·5

Mean value of $\bar{k}_3'' = 51{\cdot}5$.

Run 14

[Reactants] = 0·00200M, $[H^+] = 0{\cdot}051$M.

t (min.)	Reaction (%)	$\bar{k}_3''$ (sec.$^{-1}$ mole^{-2} l.^{2})
0	11·4	—
3·00	22·6	272
5·93	24·8	265
16·2	45·6	270
27·2	55·1	283
38·1	60·7	285
48·0	63·8	277
88·8	71·0	250

Mean value of $\bar{k}_3'' = 272$.

TABLE 7. *Diazotisation of* p*-aminophenyltrimethylammonium perchlorate at* 0°*: stoicheiometric first-order rate constants during course of reaction in different concentrations of nitrous acid in excess.*

Run 12

[Amine] = 0·000231M, $[HNO_2] = 0{\cdot}00290$M, $[H^+] = 0{\cdot}12$M.

t (min.)	Reaction (%)	$10^3\bar{k}_1''$ (sec.$^{-1}$)
2·58	34·8	2·76
4·07	47·3	2·63
5·42	58·7	2·73
7·40	70·9	2·79
10·5	79·5	2·53
15·0	87·6	2·33
24·5	93·6	3·02

Mean value of $\bar{k}_1'' = 2{\cdot}68 \times 10^{-3}$.

Run 12

[Amine] = 0·000115M, $[HNO_2] = 0{\cdot}00145$M, $[H^+] = 0{\cdot}12$M.

t (min.)	Reaction (%)	$10^3\bar{k}_1''$ (sec.$^{-1}$)
3·62	15·1	0·751
4·88	20·8	0·794
7·28	29·1	0·787
9·42	35·9	0·786
12·7	45·2	0·788
15·9	53·6	0·803
20·4	60·8	0·765
27·4	71·2	0·757
37·6	80·0	0·715

Mean value of $\bar{k}_1'' = 0{\cdot}772 \times 10^{-3}$.

The author thanks Professor E. D. Hughes, F.R.S., and Dr. J. H. Ridd for many helpful discussions, and the Department of Scientific and Industrial Research for a Maintenance Award.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER STREET,
LONDON, W.C.1.

[*Received, March 25th,* 1959.]

633. *The Substitution of Azulene by Benzyl Radicals.*

By J. F. Tilney-Bassett and William A. Waters.

Direct substitution of azulene by benzyl radicals yields 1- and 2-benzylazulene in comparable amounts and a small quantity of a pentabenzylazulene. The structures of the products have been established by direct comparison with synthetic specimens; each possible monobenzylazulene has been synthesised. For 2-benzylazulene evidence of structure was also provided by measurements of proton magnetic resonance spectra.

The production of 1- and 2-benzylazulene by homolytic substitution of azulene is not in accord with published predictions based on quantum-mechanical calculations, but is not inconsistent with previously published experimental work.

Homolytic bimolecular reactions do not involve major charge displacements, but polar effects are quite absent only if the formation of the transition state between the neutral radical and the substrate involves no net displacement of valency electrons with respect to the approaching nuclear centres. It is of interest therefore to investigate the degree to which polar effects may influence reactions between free hydrocarbon radicals and hydrocarbon molecules and already in the homolytic substitution of benzene derivatives, C_6H_5R, appreciable differences between the actions of methyl and phenyl radicals have been discerned.[1]

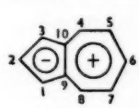
Table 1. *Theoretical calculations for azulene.*

Position	1	2	4	5	6	9
Electron density *	1·049	0·997	0·908	1·034	0·938	1·042
Electron density †	1·090	1·042	0·933	0·970	0·943	1·014
Atom localisation energy [2a] (units of β), for:						
Nucleophilic attack (N)	2·60	2·36	1·93	2·34	1·99	—
Electrophilic attack (E)	1·92	2·36	2·55	2·34	2·73	—
Free-radical attack (R)	2·26	2·36	2·24	2·34	2·36	—

* Calc. by the self-consistent field method (Julg, *J. Chim. phys.*, 1955, **52**, 377).

† Values calculated by the molecular orbital method (Berthier and Pullman, *Compt. rend.*, 1949, **229**, 761.

Unsubstituted alternant hydrocarbons, such as naphthalene, have unit π-electron density at all positions, and reactions of all types (electrophilic, nucleophilic, and homopolar) take place predominantly at the point of highest polarisability so that, though isomer ratios may vary, similarly substituted products result from all types of substitution. In contrast, non-alternant hydrocarbons, such as azulene, do not have a uniform π-electron density and different predominant positions of attack are to be expected with reagents of different types.



(I)

Theoretical computations of π-electron density and of atom localisation energies of azulene (I) for free-radical, nucleophilic, and electrophilic attack are given in Table 1.

According to theoretical approaches,[2] position 4 has the lowest calculated atom localisation energy for free radical attack, but it is closely followed by the 1-position. There is only a relatively small difference in atom localisation energies at all positions, though 2 and 6, which are the most remote from the ring-linking bond (9,10), would seem to be the least probable points of attack. Position 1 is clearly favoured for electrophilic attack and position 4 for nucleophilic attack.

To predict the reaction path for the attack on azulene of a radical having some degree of dipolar character one would have to use some combination of the data on the last line (R) of Table 1 with that of one of the preceding lines (E, N), according to the sense and magnitude of the electrical dipole associated, in the transition state, with the new developing

[1] Cowley, Norman, and Waters, *J.*, 1959, 1799.

[2] (*a*) Peters, *J.*, 1958, 1028; (*b*) Brown, *Trans. Faraday Soc.*, 1948, **44**, 984.

bond: the figures show that less than 10% of electrophilic character in the addition process would suffice to favour attack on the 5-membered ring.

The early, naive view that free radicals are essentially electrophilic with respect to olefinic bonds (Waters [3]) indicates that free-radical substitution of azulene should occur in the 5-membered ring, and probably in position 1. It has been verified experimentally that nucleophilic attack takes place at position 4 [4,5] and electrophilic attack at position 1.[5] In regard to homolytic substitution, previous workers [6,7] have shown that phenyl radicals substitute azulene to give 1-phenylazulene, but only in low yield, and that benzoyloxy-radicals yield 1-benzoyloxyazulene.[7] Study of the attack on azulene by radicals of still more different character being desirable, we have investigated its substitution by benzyl radicals, which can be regarded as alkyl radicals almost devoid of any intrinsic dipolar character.

Results

Free-radical Substitution.—Preliminary tests showed that azulene reacts immediately with 2-cyano-2-propyl radicals with loss of colour. Presumably this is due to the formation of an unstable adduct of two radicals to azulene with destruction of the fully conjugated system. With benzyl radicals, generated by the decomposition of t-butyl peroxide in boiling toluene under nitrogen,[8] some substitution did occur. In this case an initial radical addition to give $Ph{\cdot}CH_2{\cdot}C_{10}H_8{\cdot}$ can be followed by hydrogen abstraction by benzyl or t-butoxy-radicals as in the substitution of aromatic hydrocarbons by this reagent.

It was found necessary to work on a small scale and overall yields of substituted azulenes were not over 10%, but chromatography through alumina separated three products with spectra of azulene type. One of these substituted azulenes, m. p. 73—75°, was at once identified as 1-benzylazulene by its m. p., the m. p. of its 1,3,5-trinitrobenzene complex, and by the correspondence of its spectrum in the visible and the ultraviolet region with data published by Anderson and Cowles.[9] Later, through the kindness of Dr. A. G. Anderson in sending us a record of his infrared spectrum, we have been able to check the identity of our product by means of its infrared spectrum also.

The second product, m. p. 46—47°, which was separated only with difficulty, though in comparable yield, from 1-benzylazulene, was rigorously proved to be an isomer. From the study of its proton magnetic resonance spectrum by Dr. R. E. Richards and Mr. P. Higham (see Appendix) and finally by unequivocal synthesis, it was identified as 2-benzylazulene. During substantiation of this structure all the monobenzylazulenes were synthesised.

The third product, m. p. 83·5—84·5°, appears, from the analysis of its 1,3,5-trinitrobenzene adduct, to be a pentabenzylazulene.

Methylation of the sodium adduct of azulene was also investigated: this probably yields 1,3-dimethylazulene.

Whilst theoretical conclusions that can be adduced from all studies of azulene substitution must be viewed with reserve, since chemical attack always leads to extensive destruction of this ring system, the present results show that benzyl radicals attack azulene in both the 1- and the 2-position. Thus, from three different groups of workers comes evidence that three different organic radicals (alkyl, aryl, acyl) attack azulene in the negatively polarised 5-membered ring: there is as yet no clear evidence of radical attack in position 4 as predicted by certain theorists.[2]

Synthesis of the Isomeric Benzylazulenes.—2-Benzylazulene was prepared from 2-benzylindane by expanding the 6-membered ring with ethyl diazoacetate and dehydrogenating

[3] Waters, *Trans. Faraday Soc.*, 1941, **37**, 770; "The Chemistry of Free Radicals," Oxford, 1946, p. 183.
[4] Hafner and Weldes, *Angew. Chem.*, 1955, **67**, 302; *Annalen*, 1957, **606**, 90.
[5] Hafner, *Angew. Chem.*, 1958, **70**, 419.
[6] Arnold and Pahls, *Chem. Ber.*, 1956, **89**, 121.
[7] Anderson and Chang, *J. Org. Chem.*, 1958, **23**, 151.
[8] Beckwith and Waters, *J.*, 1957, 1001; Waters and Watson, *J.*, 1957, 253.
[9] Anderson and Cowles, *J. Amer. Chem. Soc.*, 1955, **77**, 4617.

the product with palladised charcoal, following the general procedure of Plattner and Wyss.[10] The 2-benzylindane was synthesised from dibenzylacetic acid by ring closure to the indanone and then Clemmensen reduction. 4-Benzylazulene was prepared by addition of benzylsodium to azulene followed by dehydrogenation of the intermediate benzyldihydroazulene with chloranil. The method is a modification of that used by Hafner and Weldes [4] for the preparation of 4-alkyl- and 4-aryl-azulenes from azulene and lithium alkyls or aryls. Hafner [5] has listed 4-benzylazulene, with physical properties corresponding to our reaction product, but has given no experimental details of his work.

6-Benzylazulene was prepared by the type of synthesis due to Hafner.[11] Treatment of 4-benzylpyridine with cyanogen bromide and *N*-methylaniline yielded the anil (II).

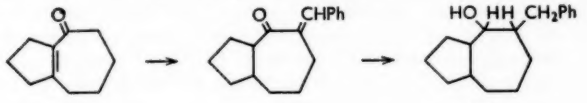
$$[PhMeN{\cdot}CH{:}CH{\cdot}C(CH_2Ph){:}CH{\cdot}CH{:}NPhMe]^+Br^- \quad (II)$$

This yielded 6-benzylazulene when treated with cyclopentadiene by a procedure similar to that [12] for the preparation of azulene.

Attempts to prepare 5-benzylazulene by a route similar to that employed for the synthesis of 6-benzylazulene were unsuccessful. The reaction between 3-benzylpyridine, cyanogen bromide, and *N*-methylaniline yielded 3-benzylpyridine hydrobromide instead of the expected anil (III), and the reaction between *N*-methylaniline and 3-benzyl-1-(2,4-dinitrophenyl)pyridinium chloride likewise failed to give this anil. Eventually 5-benzyl-

$$[MePhN{\cdot}CH{:}CH{\cdot}CH{:}C(CH_2Ph){\cdot}CH{:}NPhMe]^+Br^- \quad (III)$$

azulene was synthesised from 2-decalol. This was converted by standard methods *via* Δ^9-octalin into the ketone (IV), which was reduced catalytically to a saturated ketone and then condensed with benzaldehyde to give the benzylidene-ketone (V). Thence catalytic



(IV) (V) (VI)

reduction followed by treatment with lithium aluminium hydride yielded the alcohol (VI) together with a small proportion of a hydrocarbon. Dehydration of the alcohol and dehydrogenation of the product in the vapour phase with palladised charcoal gave a small yield of 5-benzylazulene.

TABLE 2. *Visible spectra of the benzylazulenes: shift of the absorption maximum of longest wavelength.*

Compound	Shift (mμ)	Compound	Shift (mμ)
1-Benzylazulene	+31·5	2-Benzylazulene	−20·5
5-Benzylazulene	+14·5	4-Benzylazulene	−26·0
—	—	6-Benzylazulene	−10·5
Pentabenzylazulene	+4·5		

Absorption Spectra of the Benzylazulenes.—The visible and ultraviolet absorption spectra of the isomeric benzylazulenes have been measured in hexane solution on a Cary recording spectrophotometer. Data concerning the absorption maxima are given in Table 3. Table 2 gives the shifts of the absorption maxima of longest wavelength with respect to that of azulene, and shows that Plattner's rule,[13] developed for the methylazulenes, is also applicable to the benzylazulenes. The spectral correlations, however, are not assured enough for the identification of the probable pentabenzylazulene. The infrared spectra are rather too complicated for diagnostic use without further systematic study of both band positions and intensities.

[10] Plattner and Wyss, *Helv. Chim. Acta*, 1940, **23**, 907.
[11] Hafner, *Annalen*, 1957, **606**, 79.
[12] Ziegler and Hafner, *Angew. Chem.*, 1955, **67**, 301; improved by A. G. Anderson (personal communication).
[13] Plattner, *Helv. Chim. Acta*, 1936, **19**, 858; 1941, **24**, 283; Gordon, *Chem. Rev.*, 1952, **50**, 185.

XUM

Experimental

Azulene was prepared in 32% overall yield by Anderson's modification of the synthesis by Ziegler and Hafner.[12]

Reaction of Azulene with 2-Cyano-2-propyl Radicals.—Azulene (2·0 g.) and azoisobutyronitrile (7·7 g., 3 equiv.) were heated at 100° for 2½ hr. in toluene (100 ml.) under nitrogen. The solution soon lost its blue colour. After removal of the solvent the residue was chromatographed through deactivated alumina and yielded unchanged azulene (0·1 g.) and tetramethylsuccinonitrile (2·1 g., 33%), together with a gum which failed to give any azulene derivative with chloranil in hot benzene.

Reaction of Azulene with Benzyl Radicals.—Azulene (4·0 g.), t-butyl peroxide (11 g.), and toluene (250 ml.) were refluxed together under nitrogen for 70 hr. After removal of the solvent the residue was passed in light petroleum (b. p. 40—60°) through alumina (type H) and gave unchanged azulene (0·5 g.) and then a blue oil (0·6 g.). Crystallisation of the latter from light petroleum yielded 1-benzylazulene (0·095 g.), m. p. 73—75°, identified by means of its visible, ultraviolet, and infrared spectra and as 1,3,5-trinitrobenzene adduct, m. p. 96—97° [5,9] (Found: C, 64·5; H, 4·4; N, 9·3. Calc. for $C_{23}H_{17}O_6N_3$: C, 64·0; H, 4·0; N, 9·7%).

Crystallisation of the more soluble portions of the blue oil gave dark blue needles (0·080 g.), m. p. 46—47°, of *2-benzylazulene* [Found: C, 93·2; H, 7·0%; *M* (isothermal distillation [14]), 216, 220. $C_{17}H_{14}$ requires C, 93·5; H, 6·5%; *M*, 218]. Its *1,3,5-trinitrobenzene adduct* had m. p. 125—126° (Found: C, 64·0, 64·3; H, 4·7, 3·9; N, 9·4. $C_{23}H_{17}O_6N_3$ requires C, 64·0; H, 4·0; N, 9·7%). The absorption spectrum of this compound was identical with that of synthesised 2-benzylazulene.

The uncrystallised portion of the blue oil was collected together and analysed spectrophotometrically [15] in hexane; it contained 37% of 1-benzylazulene, 40% of 2-benzylazulene, and 23% of material that did not absorb in the visible region. Elution of the alumina with 5% of benzene in light petroleum gave blue needles, m. p. 83·5—84·5° (0·08 g.) (Found: C, 92·9; H, 6·3. $C_{45}H_{38}$ requires C, 93·1; H, 6·9%), which gave a chocolate-coloured trinitrobenzene adduct, m. p. 79—80° (Found: C, 77·3; H, 5·2; N, 5·2. $C_{51}H_{41}O_6N_3$ requires C, 77·4; H, 5·2; N, 5·3%); this corresponds to a *pentabenzylazulene*.

Reaction of Sodium with Azulene.—Azulene (0·5 g.) was shaken for 3½ days at room temperature with sodium (0·4 g.), 1,2-dimethoxyethane (7 ml.), and a little powdered glass. The mixture, under nitrogen, was then treated with methyl iodide (1·9 ml.), benzene was added, and the filtered solution was refluxed for 3 hr. with chloranil (1 g.). After removal of the solvent the residue, in light petroleum, was chromatographed through alumina. It gave 0·08 g. of a blue gum which, after treatment with trinitrobenzene (0·12 g.) in boiling ethanol gave black needles (0·06 g.), m. p. 162—164° (Found: C, 58·9; H, 4·2; N, 12·1. Calc. for $C_{18}H_{15}O_6N_3$: C, 58·6; H, 4·1; N, 11·4%). This corresponds to the *adduct* of a dimethylazulene. Passage of this adduct in ethanol through alumina regenerated a blue oil (0·02 g.), which by crystallisation from light petroleum at −50° gave a trace of solid, m. p. 39—48°. The visible spectrum, in ethanol has maxima at wavelengths corresponding to that of 1,3-dimethylazulene, m. p. 54° (cf. Gordon [13]):

Peak positions found (mμ)	780	742	697	666	633	611	585
Δλ from that of azulene (mμ)	88	86	68	68	56	55	44
Δλ for 1,3-dimethylazulene	73	89	72	69	58	53	45

Synthesis of 2-Benzylazulene.—Dibenzylacetic acid, m. p. 88—89°, was prepared in 83% yield (3 stages) from benzyl chloride and ethyl malonate. The acid (200 g.) was converted, with thionyl chloride, into its acyl chloride which, in light petroleum (b. p. 80—100°; 1 l.), was treated with aluminium chloride (200 g.) and heated at 100° until reaction ceased. After decomposition with ice *2-benzylindan-1-one* (75%), b. p. 154—160°/0·4 mm., was isolated in the usual manner [*2,4-dinitrophenylhydrazone*, m. p. 195—197° (decomp.) (Found: C, 65·1; H, 4·4; N, 14·2. $C_{22}H_{18}O_4N_4$ requires C, 65·7; H, 4·5; N, 13·9%)]. Reduction of 2-benzylindan-1-one with amalganated zinc and hydrochloric acid gave a 77% yield of 2-benzylindane, b. p. 104—106°/0·2 mm. (Found: C, 91·8; H, 7·8. Calc. for $C_{16}H_{16}$: C, 92·2; H, 7·8%). Ethyl diazoacetate (6·4 g.) was added dropwise in 20 min. to 2-benzylindane (59 g.) at 130°. The mixture was then heated during 30 min. to 160°, kept thereat for 1½ hr., and distilled through a column. The unchanged 2-benzylindane, b. p. up to 125°/0·1 mm., was treated, as before, with a further

[14] Niederl, Kasanov, Kisch, and Subba Rao, *Mikrochem.*, 1949, **34**, 132.
[15] Dewar and Urch, *J.*, 1957, 345.

equal portion of ethyl diazoacetate, and the whole process was repeated a further 3 times. The combined distillation residues were then distilled at 130—190°/0·2 mm., yielding a brown oil (26·3 g.), 44·5 g. of 2-benzylindane being recovered.

This oil was refluxed for 2 hr. with potassium hydroxide (10 g.) in water (20 ml.) and ethanol (50 ml.). The acid was separated, by ether, as a dark viscous oil (10·5 g.). This was distilled rapidly from 10% palladised charcoal (1·1 g.), yielding a deep blue liquid, chromatography of which, in light petroleum, through alumina gave some azulene and crude 2-benzylazulene (0·7 g.) which, on further crystallisation from light petroleum (40—60°), formed intensely blue crystals, m. p. 48° (0·37 g.), mixed m. p. 46—47° with the benzylation product of azulene. The residue from the crystallisation of the authentic material gave, with trinitrobenzene in ethanol, an adduct, m. p. 121—124°, identical with that of the benzylation reaction. The infrared, visible, and ultraviolet absorption spectra of the two 2-benzylazulenes were, in similar solvents, identical.

Synthesis of 4-*Benzylazulene.*—A mixture of toluene (1 ml.) and chlorobenzene (0·9 ml.) was added slowly, with vigorous stirring, to powdered sodium (0·5 g.), suspended in toluene (2·9 ml.) at 30—40° under dry nitrogen. After 1 hour's stirring, the mixture was refluxed for 2 hr. to convert phenylsodium into benzylsodium,[16] then treated with azulene (0·5 g.) in toluene (3 ml.), stirred at 100° for another 10 min., cooled, and decomposed with ice-water. The organic layer was separated, washed with dilute acid, dried ($MgSO_4$), and refluxed for 90 min. with chloranil (1·5 g.) in benzene (50 ml.). After removal of the solvent, chromatography of the residue gave 4-benzylazulene (0·14 g.), m. p. 54—55°, after crystallisation from light petroleum (b. p. under 40°) at −30° (Hafner [5] gives m. p. 55—57°) (Found: C, 93·4; H, 6·5. Calc. for $C_{17}H_{14}$: C, 93·5; H, 6·5%). Its trinitrobenzene complex had m. p. 125—126° (from ethanol) (Found: C, 64·2; H, 4·1; N, 9·9. Calc. for $C_{23}H_{17}O_6N_3$: C, 64·0; H, 4·0; N, 9·7%).

Synthesis of 6-*Benzylazulene.*—4-Benzylpyridine [17] (6·15 g.) and *N*-methylaniline (7·8 g.) in dry ether (30 ml.) at 0° were treated, with stirring, during 20 min., with cyanogen bromide (3·9 g.) in ether (20 ml.). After the mixture had been stirred overnight, ether was decanted from the red gum which had been formed. This crude 3-*benzyl*-N-*methyl*-5-(N-*methylanilino*)-N-*phenylpenta*-2,4-*dienylideneammonium bromide* (II) was dissolved in a little ethanol, precipitated with ether, and further purified in the same way; it formed pink crystals, m. p. 101° (decomp.) (6·64 g.), containing 1 mol. of ethanol of crystallisation (evident from the infrared spectrum) (Found: C, 67·6; H, 6·4. $C_{26}H_{27}N_2Br,C_2H_5{\cdot}OH$ requires C, 67·6; H, 6·7%).

Cyclopentadiene (1·83 g.) was stirred with sodium methoxide (0·96 g.) in diethylene glycol (80 c.c.) under nitrogen for 5 min., then the above salt (6·25 g.) was added. After a further hour's stirring at room temperature the mixture was diluted with diethylene glycol (240 ml.), heated to 220°, and distilled with superheated steam. The distillate was diluted with a large bulk of water, and the precipitate of 6-*benzylazulene* was collected. A further quantity was obtained by diluting the distillation residue with water and extracting it with light petroleum (total yield, 0·58 g.). After crystallisation from light petroleum the 6-benzylazulene had m. p. 99—100° (Found: C, 92·9; H, 6·6. $C_{17}H_{14}$ requires C, 93·5; H, 6·5%). Its *trinitrobenzene adduct* had m. p. 109—110° (Found: C, 64·5; H, 4·2; N, 9·4. $C_{23}H_{17}O_6N_3$ requires C, 64·0; H, 4·0; N, 9·7%).

Synthesis of 5-*Benzylazulene.*—(a) *Attempted synthesis from* 3-*benzylpyridine.* Treatment of 3-benzylpyridine [18] with methylaniline and cyanogen bromide, as described above, gave 3-benzylpyridine hydrobromide, m. p. 143—145° (72%). By refluxing 3-benzylpyridine and 1-chloro-2,4-dinitrobenzene in benzene a 93% yield of 3-*benzyl*-1-(2,4-*dinitrophenyl*)*pyridinium chloride* was obtained, having m. p. 105—107° (from chloroform) (Found: C, 55·1; H, 4·2; N, 11·0; Cl, 9·4. $C_{18}H_{14}O_4N_3Cl,H_2O$ requires C, 55·5; H, 4·1; N, 10·8; Cl, 9·1%). This substance scarcely reacted with *N*-methylaniline in boiling ethanol, the pyridinium salt being recoverable as the perchlorate, in 50% yield after 6 hr. and 28% after 17 hr. The *perchlorate* had m. p. 209—210° (Found: C, 50·1; H, 3·5; N, 9·0; Cl, 7·6. $C_{18}H_{13}O_4N_3,HClO_4$ requires C, 49·6; H, 3·2; N, 9·6; Cl, 8·1%).

(b) *Synthesis from* β-*naphthol.* Δ^9-Octalin, prepared from 2-decalol,[19] was converted into cyclodecane-1,6-dione by treatment with hydrogen peroxide in formic acid, followed by

[16] Morton and Massengale, *J. Amer. Chem. Soc.*, 1940, **62**, 121; Morton, Massengale and Gibbs, *ibid.*, 1941, **63**, 325.
[17] Benkesen and Holden, *ibid.*, 1951, **73**, 5861.
[18] Tschitschibabin, *Ber.*, 1903, **36**, 2711.
[19] Linstead, Wang, Williams, and Errington, *J.*, 1937, 1139.

TABLE 3. *Ultraviolet and visible spectra of the benzylazulenes in hexane solution (wavelengths in* mμ *and* log ε).

Azulene		1-Benzyl-		2-Benzyl-		4-Benzyl-		5-Benzyl-		6-Benzyl-		Pentabenzyl	
697·5	2·25	729	2·03	677	2·11	671·5	2·21	712	2·13	687	2·16	702	2·27
665*i*	2·15	—	—	—	—	—	—	—	—	—	—	—	—
659	2·18	692sh	2·09	650	2·07	—	—	674	2·16	649	2·16	675*i*	2·29
631·5	2·51	657·5	2·43	614	2·45	613	2·58	644	2·46	622·5	2·47	633·5	2·67
—	—	—	—	605sh	2·39	—	—	—	—	—	—	—	—
603·5	2·47	627	2·43	590	2·37	586sh	2·62	612	2·44	595	2·45	611·5	2·65
579	2·51	601·5	2·50	570	2·48	570	2·64	589	2·47	571·5	2·50	586	2·73
557	2·42	579*i*	2·42	564sh	2·47	547*i*	2·55	567*i*	2·39	551s	2·42	—	—
537	2·33	557*i*	2·34	523	2·33	—	—	547*i*	2·30	532s	2·33	545*i*	2·58
519	2·20	535*i*	2·22	—	—	—	—	526*i*	2·16	512*i*	2·20	—	—
352	3·05	361	3·58	358	3·12	355	3·09	356	3·40	—	—	366	3·32
340	3·67	345	3·72	345	3·79	342·5	3·65	344	3·60	346	3·83	350	4·19
336·5	3·61	—	—	—	—	339	3·57	340	3·64	—	—	—	—
332·5	3·43	—	—	—	—	—	—	331·5	3·44	338	3·60	—	—
326	3·51	336	3·52	330	3·70	330	3·48	328	3·43	330	3·65	334	3·87
322	3·43	331	3·48	—	—	328	3·48	324·5	3·39	324	3·47	326*i*	3·64
315	3·29	322	3·30	318*i*	3·30	318*i*	3·27	318	3·22	319	3·41	320*i*	3·57
296	3·63	298	3·81	302	3·80	299	3·63	298	3·69	299·5	3·83	303	4·17
279	4·76	289	4·65	286	5·03	289·5	4·74	283s	4·66	—	—	—	—
274	4·79	285	4·78	—	—	279	4·72	278·5	4·70	285	4·95	290	5·19
269·5	4·79	279	4·80	276	5·05	275*i*	4·69	275*i*	4·63	279·5	4·91	283	5·13
236	4·30	237	4·31	237	4·30	239	4·54	242	4·21	237	4·27	240	4·59

sh indicates a shoulder, not a peak. *i* indicates a point of inflexion.

TABLE 4. *Infrared absorption maxima (cm.$^{-1}$) of the benzylazulenes.*

Azulene	1-Benzyl	2-Benzyl	4-Benzyl	5-Benzyl	6-Benzyl	Pentabenzyl
1388	1393	1390	1360	1393	1387	1380
—	—	1319	—	—	1300	—
1288	1291	1290	(1253w)	—	—	1277
1195s	—	1195s	1215	1208	1195	1195w
—	—	—	1120w	1177w	—	—
—	1072m	1073m	1067	1079w	1075	1072
1051	—	—	—	1046w	1050	—
—	1028	1030	1029	1027	1028	1027
—	—	—	—	1010	—	—
960	—	—	960	987	961w	983
942	943	943	—	948	—	—
—	920w	928	915w	922	927	—
895m	885w	891s	—	890w	—	885w
819m	—	827m	815	825w	842	—
—	—	—	—	810w	807	—
—	—	793vs	—	775s	795	780
763s	765	764s	757s	755s	747	—
719m	728s	725s	727	742	717	726
—	694	697	695	696	693	695

Apart from 5-benzylazulene, which was examined in paraffin paste, the spectra were measured in carbon disulphide solution.

The intense band at 693—697 cm.$^{-1}$ is due to the phenyl group; another phenyl adsorption band in the 730—770 cm.$^{-1}$ region overlaps with a broadish band of the azulene system.

oxidation of the resulting 9,10-dihydroxydecalin with lead tetra-acetate by Dev's method.[20] The diketone with sodium carbonate yielded biçyclo[5,3,0]dec-1(7)-en-2-one,[21] which on hydrogenation at atmospheric pressure with 5% palladised charcoal furnished decahydroazulen-4-one.[22] This ketone (7·3 g.) and benzaldehyde (6 g.) were refluxed for ½ hr. with potassium hydroxide (2 g.) in ethanol (30 ml.) and, after cooling and dilution with water, *5-benzylidenedecahydroazulen-4-one* was isolated and crystallised from ethanol (m. p. 73°) (Found: C, 84·4; H, 8·8. $C_{17}H_{20}O$ requires C, 84·9; H, 8·4%). This (5·8 g.) was hydrogenated in ethanol (50 ml.) at atmospheric pressure with Adams catalyst and, after removal of the catalyst and the ethanol, the product was reduced with lithium aluminium hydride in the normal way. Chromatography of the product gave a colourless oily hydrocarbon (1·5 g.), probably 5-benzyldecahydroazulene, and then an oil (2·9 g.) having the infrared spectrum of an alcohol.

[20] Dev, *J. Indian Chem. Soc.*, 1954, **31**, 1.
[21] Anderson and Nelson, *J. Amer. Chem. Soc.*, 1951, **73**, 232.
[22] Hückel and Schnitzpahn, *Annalen*, 1933, **505**, 274.

Crystallisation of the latter from light petroleum yielded colourless needles (0·4 g.), m. p. 79—80° of one of the stereoisomers of *5-benzyldecahydroazulen-4-ol* (Found: C, 83·5; H, 9·8. $C_{17}H_{24}O$ requires C, 83·5; H, 9·9%).

The alcohol (2·5 g.) was heated at 180° for 10 min. with potassium hydrogen sulphate (2·4 g.), then cooled, treated with water, and extracted with light petroleum. The dried petroleum solution on evaporation gave a brown oil (2·2 g.) which was distilled slowly, in a stream of nitrogen under reduced pressure, through a tube containing 5% palladised charcoal (0·4 g.) and asbestos fibre (0·4 g.) at 320—325°. A blue oil (1·6 g.) was obtained and this by chromatography gave 1·56 g. of a colourless oil and 0·035 g. of a blue oil. Crystallisation of the latter from light petroleum (b. p. <30°) gave 5-benzylazulene, m. p. 54·5—55·5°. Its *trinitrobenzene adduct* crystallised from ethanol as brown needles, m. p. 103—105° [Found (for 0·824 mg.): C, 63·2; H, 4·7. $C_{23}H_{17}O_6N_3$ requires C, 64·0; H, 4·0%).

Appendix

By P. Higham and R. E. Richards
(Physical Chemical Laboratory, Oxford)

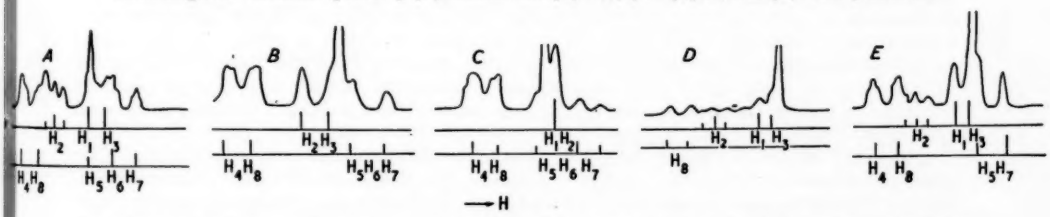
The following report relates to the radical-substitution product, m. p. 46—47°, of azulene, for which at that time only ultimate analysis was available.

The synthesis of authentic 2-benzylazulene was completed later, the identity of the two being then confirmed.

The proton magnetic resonance spectra of the radical product and of a number of benzylazulenes were investigated. The limited quantity of material made it necessary to use spherical samples. The solution of the material in chloroform or carbon disulphide was contained in a bubble in a gelatine matrix or in a 3 mm. glass sphere with capillary inlet.[23] The spectra were measured with a high-resolution apparatus, using a fixed frequency of 29·9200 Mc./sec. and a permanent magnet.[24] The work of Schneider, Bernstein, and Pople [25] on azulene was used in assigning the lines.

In addition to the azulene spectrum, the radical product gave lines for the CH_2 and C_6H_5 hydrogen atoms of the benzyl group. There was no evidence of a line for a CH_3 group which should give a resonance at higher applied fields. To check the sensitivity of the apparatus a sample containing 3 mg. of toluene was used for comparison. The only feature not present in the other benzylazulenes was a large peak on the high applied-field side of the phenyl peak.

Proton magnetic resonance spectra of (*A*) *azulene and* (*B*) 1-, (*C*) 2- (*D*) 5-, *and* (*E*) 6-*benzylazulene.*



Its intensity was approximately equal to that of the peak due to the CH_2 group. The only situation in which a single peak of this intensity could be produced in an azulene is for two protons to have the same unsplit resonance frequency. This is the case with the hydrogens in the 1- and the 3-position of 2-benzylazulene. Further, the radical product gave the absorption spectrum expected for an unsubstituted 7-membered azulene ring. All these results are most consistent with the radical product's being 2-benzylazulene.

Spectra measured are reproduced herewith.

One of us (J. F. T.-B.) thanks the Department of Scientific and Industrial Research for a Maintenance Grant.

The Dyson Perrins Laboratory, Oxford. [*Received, March 2nd,* 1959.]

[23] Higham and Richards, *Proc. Chem. Soc.*, 1959, 128.
[24] Leane, Richards, and Schaefer, *J. Sci. Instr.*, 1959, **36**, 230.
[25] Schneider, Bernstein, and Pople, *J. Amer. Chem. Soc.*, 1958, **80**, 3497.

XUM

634. *Metallic Salts as Promoters in Hydrogenation with Platinum Oxide Catalysts.*

By E. B. Maxted and Sayeed Akhtar.

The effect of adding small quantities of various metallic chlorides to liquid-phase hydrogenation systems in the presence of platinum oxide catalysts has been studied. If this addition is made before the reduction of the platinum oxide to metal, promotion effects involving an increase in the hydrogenation rate up to over ten times its unpromoted value and a continuous hydrogenation path have been obtained for the reduction of valeraldehyde and acetone.

It is known that many metallic ions which are toxic towards platinum-metal catalysts in the liquid-phase hydrogenation of unsaturated C–C bonds are capable of acting as promoters in the reduction of aldehydes, ketones, or certain acid anhydrides if platinum oxide, initially unreduced, is used as the catalyst.[1] In addition to a large rise in the hydrogenation rate, a suppression of the series of halts which recur in the hydrogenation of aldehydes or the like, as a result of the elimination of traces of oxygen from the system, may also occur. Ferric chloride was in this earlier work found to be the most active promoter of a large number of substances tested.

This effect has now been studied in greater detail, mainly in order to try to extend the range of the promoters examined. It has been found that stannous chloride, which does not appear to have been previously used, possesses at its optimum concentration a very much higher promoting power than that given by ferric salts. Further, very appreciable promotion has also been obtained, both with stannous chloride and to a lesser degree with ferric chloride, in the hydrogenation of ethyl cinnamate with a platinum oxide catalyst.

Experimental

The catalyst used throughout the present work was taken from a stock of platinum dioxide, containing 83·5% of platinum. Liquid-phase hydrogenation, usually of valeraldehyde, was carried out, at atmospheric pressure and at 20°, in a hydrogenation shaker operating under standardised conditions. In view of the known effect [2] of traces of oxygen on the rate of hydrogenation, the electrolytic hydrogen employed, which had originally an oxygen content of less than 50 parts per million, was further purified by passage over heated platinum immediately before its employment for hydrogenation. The metallic chlorides, in general, were applied in ethyl alcohol solution.

Promoting Effect of Various Metallic Chlorides in the Reduction of Valeraldehyde.—As a preliminary survey, the relative effect of a constant small amount (10^{-5} mole) of a number of the more active metallic chlorides on the hydrogenation rate of 1 c.c. of valeraldehyde, in 9 c.c. of alcohol, by 0·025 g. of stock platinum oxide is shown in Fig. 1. In order to avoid overcrowding in the curves of this Figure, the effects of some less active promoters are given separately in Table 1.

Table 1.

Promoter	None	$ZnCl_2$	$CrCl_3$	$CuCl_2$	$MnCl_2$	$AlCl_3$
H_2 absorbed (c.c.) in 1 hr.	12	34	29	27·5	25	23·5

It will be seen that stannous chloride is, under the conditions used, by far the most effective promoter tested, 127 c.c. of hydrogen being absorbed in an hour, compared with 92 c.c. for ferric chloride and only 12 c.c. in a blank run without a promoter. The relatively small promoting effect of stannic chloride, compared with that of the stannous salt, is to be noted. This point is of interest in connection with Carothers and Adams's observation [1] of no effective

[1] Carothers and Adams, *J. Amer. Chem. Soc.*, 1925, **47**, 1047.
[2] Willstätter and Jacquet, *Ber.*, 1918, **51**, 767.

difference between the promoting activities of ferrous and ferric chlorides in the hydrogenation of benzaldehyde. In view of the lower promoting effect of stannic chloride than of the stannous salt, solutions of the latter gradually lose accelerating power on storage. Accordingly, in order to minimise oxidation, alcohol through which nitrogen had been passed was used in the preparation of the stannous chloride solution; and, with this precaution, any fall in the promoting power of a solution of stannous chloride only became noticeable after about 4 days. The low promoting power of Cr^{3+} and of Zn^{2+} should also be noted. With magnesium chloride some turbidity in the solution hydrogenated was observed, owing probably to slight hydrolysis; and the small increase in the hydrogenation rate may be due to a support effect since both the promotion and the turbidity disappeared on addition of a small quantity of hydrochloric acid.

The promoting effect of stannous chloride appears to be specially high for hydrogenation in alcoholic solutions. Thus, on changing the solvent to ethyl acetate, promotion by 10^{-5} mole of stannous chloride led to a hydrogen absorption of 52 c.c. in an hour, compared with 12 c.c.

FIG. 1 *Activation of* PtO_2 *catalyst by metallic salts.*

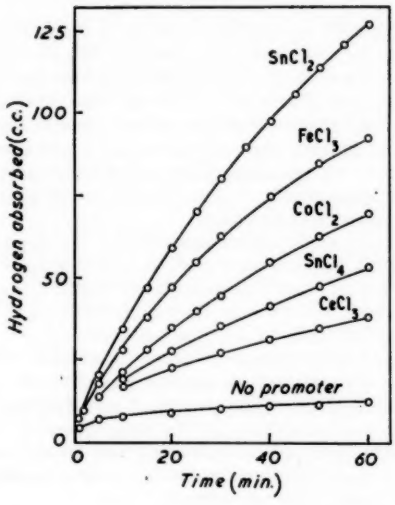
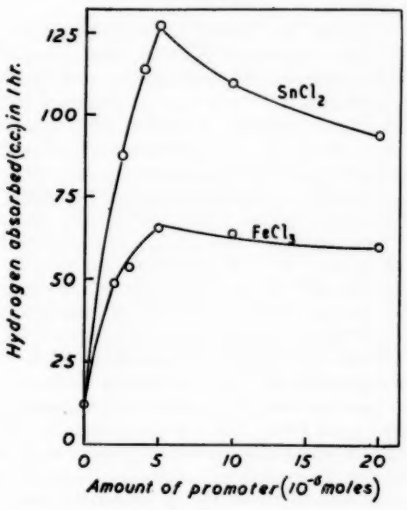


FIG. 2.



in a corresponding blank run. These figures should be contrasted with those given in Fig. 1 for the increase in the velocity obtained for the hydrogenation of valeraldehyde in alcohol.

Conditions for Maximum Promotion.—The observed variation of the promoting effect with the concentration of stannous and ferric chlorides is given in Fig. 2, the hydrogenation being, however, carried out with a stock of valeraldehyde which was not identical with that used for Fig. 1. It will be seen that maxima in the promotion occur, with both promoters, at a concentration of about 5×10^{-6} mole and that, at this optimum concentration, the reaction rates correspond with the absorption of 125 c.c. of hydrogen per hr. for stannous chloride and 68 c.c. for ferric chloride, the unpromoted value being 10·5 c.c. per hr. The position of these maxima will of course change with the nature and concentration of the unsaturated substance and with the area of the catalyst surface, in each case on account of changes in the distribution of the unsaturated substance between the adsorbed and the free liquid phases.

Effect of Mixed Promoters.—The effect of a given molecular quantity of two promoters was in general intermediate between that exercised by the same quantity of each promoter separately. Thus a hydrogenation system, as used for Fig. 1 but containing 10^{-5} mole of both stannous and ferric chlorides, absorbed 109 c.c. of hydrogen in the first hour, compared with adsorptions of 127 and 92 c.c., respectively, with stannous chloride and ferric chloride alone. A similar intermediate absorption was also obtained for stannous and manganous chlorides and their mixture. This is shown in the first part of Table 2. The second part of this table

contains figures for the hydrogen absorption obtained with mixtures of stannous and cerous chlorides, the amount of the stannous salt being kept constant at its optimum value and the concentration of cerous chloride being varied.

TABLE 2.

Promoter (moles)	Hydrogen absorption (c.c.) in 1 hr.	Promoter (moles)	Hydrogen absorption (c.c.) in 1 hr.
10^{-5} $SnCl_2$	127	5×10^{-6} $SnCl_2$	123
10^{-5} $MnCl_2$	25	5×10^{-6} $CeCl_3$	33
10^{-5} $SnCl_2 + 10^{-5}$ $MnCl_2$	88	5×10^{-6} $SnCl_2 + 5 \times 10^{-6}$ $CeCl_3$	94
		5×10^{-6} $SnCl_2 + 10^{-5}$ $CeCl_3$	46
		5×10^{-6} $SnCl_2 + 2 \times 10^{-5}$ $CeCl_3$	38

Promotion in Other Hydrogenation Systems.—In addition to the above work, the use of stannous chloride in the hydrogenation of a ketone, ethyl cinnamate, and cyclohexene was studied.

Ketones are known to be hydrogenated rather slowly by platinum oxide at room temperature. Thus a charge containing 1 c.c. of acetone, 9 c.c. of alcohol, and 0·025 g. of platinum oxide underwent hydrogenation, in the absence of a promoter, at a very low and gradually decreasing rate, only 7·6 c.c. of hydrogen being absorbed in 20 min., by which time the reaction had almost stopped. However, after the addition of 10^{-5} mole of stannous chloride to a similar charge, absorption of hydrogen took place at an approximately constant rate of 3 c.c. per min. until 200 c.c. had been absorbed, following which the rate gradually fell until approximately the theoretical volume of hydrogen had been taken up in about 4 hr. There was, in the presence of the promoter, no intermediate halt, and no reactivation was necessary.

The hydrogenation of ethyl cinnamate by platinum oxide differs from that of aldehydes and ketones since it proceeds smoothly to completion without intermediate reactivation of the catalyst. Thus a standard charge containing 1 c.c. of ethyl cinnamate absorbed 55 c.c. of hydrogen in 30 min. This absorption was raised to 68 c.c. in 30 min. by the inclusion of 10^{-5} mole of ferric chloride, and up to 96 c.c. by the same quantity of stannous chloride.

With cyclohexene and platinum oxide a far higher hydrogenation velocity is reached and an approximately linear course is followed. In this case, a slight promotion was obtained if 10^{-5} mole of stannous chloride was included in the system (1 c.c. of cyclohexene, 9 c.c. of alcohol, 0·025 g. of PtO_2), but a slight poisoning effect for a similar addition of the same quantity of ferric chloride, the times for complete hydrogenation being 12 min. in the blank run, 10 min. in the run promoted by stannous chloride, and 13·5 min. for ferric chloride. These figures correspond to about 17% acceleration and to 12% retardation, respectively.

Pre-reduced platinum black, on the other hand, was poisoned both by stannous chloride and by ferric chloride. Thus, in the reduction of 1 c.c. of cyclohexene in alcohol, by 0·025 g. of metallic platinum, the volume of hydrogen absorbed after 10 min. was 225 c.c. in the blank run, the corresponding values being 208 and 15 c.c. with 10^{-5} mole of stannous and ferric chloride respectively.

Variation of the Promotion Effect with Temperature.—This was studied for the hydrogenation of valeraldehyde in a system containing 0·025 g. of platinum oxide, 1 c.c. of valeraldehyde, 9 c.c. of alcohol, and, in the promoted series, 10^{-5} mole of stannous chloride. The hydrogen absorption after 30 min., at temperatures between 0° and 35°, is shown in Table 3, the volumes being corrected to N.T.P.

TABLE 3.

Temp.		0°	20°	25°	30°	35°
C.c. of hydrogen absorbed in 30 min.	Unpromoted system ...	9·3	10·6	11·1	8·3	8·5
	Promoted system	42·0	79	82	69·0	60

In addition to the rather large promotion effect in the second series, the hydrogenation rate passes in both cases through a maximum at 25°. About 5 c.c. of the above volumes correspond in each case to hydrogen required for the reduction of the platinum oxide. Accordingly, the smallness of the net absorption probably accounts for the reversal in sequence in the absorption at 30° and 35° in the unpromoted series.

Discussion.—It is known that, if platinum black is deprived of oxygen by use in the catalytic hydrogenation of aldehydes or acid anhydrides such as phthalic anhydride, the activity of the catalyst becomes reduced to a low order, but can be restored by treatment with oxygen:[2] complete hydrogenation of such substances usually necessitates a series of alternate hydrogenations and revivals with oxygen. This revival with oxygen has been found by us also to apply in the hydrogenation of unsaturated C–C bonds, *e.g.*, in the hydrogenation of ethyl cinnamate with platinum black which had previously been freed from oxygen by its use in the hydrogenation of phthalic anhydride (unpublished work). Similar effects in oxygen-free systems also occur in hydrogenation with platinum oxide catalysts,[3] and the necessity for reactivation by treatment with oxygen can be delayed or eliminated by the addition of suitable promoters. It may be noted that the promoters used are in all cases very small quantities of metallic salts known to be toxic in catalytic hydrogenation on platinum; and it appears probable that the action takes place by retarding the autocatalytic reduction of the platinum oxide to metal in such a way as to prolong the period during which highly active nascent platinum is being produced. Further, since the reduction of the platinum oxide to metal is an exothermic process, this should present continuously, during the reduction, freshly produced platinum having a localised temperature higher than that of the surrounding liquid. Moreover, after the reduction of the platinum oxide to metal, the poison should reduce the activity of the metallic platinum in such a way as to induce a reaction path which curves gradually towards the time axis, as was in most cases obtained.

On rise of the gross reduction temperature, the time of this production of highly active platinum is decreased, so that the period of greater activity is shortened, *i.e.*, the volume of hydrogen taken up by the valeraldehyde after a given time decreases with temperature, as was shown in Table 3. This decrease is, however, superimposed on the ordinary increase in the hydrogenation velocity with temperature. By reason of these opposed factors, the amount of hydrogen taken up after a given time passes through a maximum as the temperature is increased, and this rise and subsequent fall should be more pronounced in a promoted than in an unpromoted system. Further factors in this subsequent fall in the reaction rate are to be found in the decrease with temperature of the solubility of hydrogen in the solvent and of its adsorption on the catalyst.

One of us (S. A.) acknowledges with thanks the grant of a Research Scholarship under the Colombo Plan.

Department of Physical and Inorganic Chemistry,
The University, Bristol.

[*Received, April 17th,* 1959.]

[3] Vorhees and Adams, *J. Amer. Chem. Soc.*, 1922, **44**, 1397.

635. *Aromatic Alkylation. Part III.* Comparison of the Reactivities of Some Aromatic Compounds towards Diphenylcarbonium Ions.*

By D. Bethel, V. Gold, and T. Riley.

The rate of reaction of diphenylmethanol with benzene, anisole, and the three dimethoxybenzenes in acetic acid–sulphuric acid solutions show a similar dependence on solvent acidity and, even for the most reactive compound (*m*-dimethoxybenzene), the reaction remains of first order with respect to both diphenylmethanol and the aromatic compound. The relative reactivities of the aromatic compounds fall into a sequence similar to those of these compounds towards bromination in acetic acid, but the effect of substitution on the reactivity is more marked in the latter case. It is shown that the measurements cannot be analysed satisfactorily on the assumption of independent substituent effects to yield information about the activating or deactivating influence of the methoxyl group.

The formation of 4-methoxytriphenylmethane by acid-catalysed interaction of diphenylmethanol (or its acetate) and anisole is a bimolecular reaction (sometimes also denoted[1] by the symbol S_N2C^+) between rapidly formed carbonium ions and anisole,[2] *i.e.*:

$$Ph_2CH^+ + ArH \longrightarrow Ph_2CHAr + H^+$$

It seemed possible that an increase in the reactivity of the aromatic compound might lead to the observation of a different mechanism of aralkylation. There are the possibilities of either an S_N1 reaction in which the ionisation of the aralkylating agent, $Ph_2CHX \longrightarrow Ph_2CH^+ + X^-$, controls the rate or of a bimolecular reaction between the un-ionised aralkylating agent (or its conjugate acid) and the aromatic compound. These two cases would correspond respectively to the unimolecular zero-order nitrations in which the generation of NO_2^+ ions is rate-controlling[3] and to nitration by the species HNO_3 (or $H_2NO_3^+$).[4]

The experiments now reported were carried out with the dual objective of (*a*) investigating the substituent effects on the aromatic compound, taking as main example the effect of introducing one or two methoxyl groups into the aromatic nucleus, and (*b*) examining whether the expected enhancement of reactivity thus produced is sufficient to change the mechanism of the reaction in the above-mentioned manner. In view of the reported very much faster bromination of *m*-dimethoxybenzene[5] than of anisole, it was considered that *m*-dimethoxybenzene was perhaps one of the compounds most likely to exhibit a different mechanism of aralkylation if it can be realised with diphenylmethanol in acetic acid solution, *i.e.*, under conditions which appear favourable to the rapid generation of carbonium ions.

The alternative mechanisms would differ from the S_N2C^+ mechanism observed so far, not only in the order with respect to ArH, but also in their dependence on the solvent acidity. The S_N1 and S_N2 reactions involving $Ph_2C{\cdot}OH_2^+$ in the rate-controlling step are expected to depend on Hammett's acidity function H_0 much less steeply than the S_N2C^+ reaction. The rate should follow the relation, $\log k = \text{Constant} - H_0$, if we neglect the explicit consideration of effects of ion association, as seems justified in this context.[2,6,7]

* Part II, *J.*, 1958, 1930.

[1] Gelles, Hughes, and Ingold, *J.*, 1954, 2928.
[2] Bethell and Gold, *Chem. and Ind.*, 1956, 741; *J.*, 1958, 1905.
[3] Benford and Ingold, *J.*, 1938, 929; Hughes, Ingold, and Reed, *J.*, 1950, 240.
[4] Halberstadt, Hughes, and Ingold, *J.*, 1950, 2441.
[5] de la Mare and Robertson, *J.*, 1943, 279; de la Mare and Vernon, *J.*, 1951, 1764.
[6] Bethell and Gold, *J.*, 1958, 1930.
[7] Cf. Satchell, *J.*, 1958, 1915, 1927; Bethell, Gold, and Satchell, *J.*, 1958, 1918.

XUM

Experimental

The method of purification of acetic acid and diphenylmethanol, and the preparation of indicators and of solvent mixtures, were as described earlier.[2,6] All rate comparisons reported in this paper relate to uniform batches of solvent, and to a constant concentration of water (0·55M).

o- and *p*-Dimethoxybenzene were purified by steam-distillation and crystallisation from benzene (at 0°) and ethanol, respectively (to m. p. 22° and 56°). *m*-Dimethoxybenzene and

Table 1. *Results of kinetic measurements. Velocity constants for diphenylmethylation at 25°.*

Anisole.[*] $[ArH]_0 = 2·57 \times 10^{-2}$M; $[Ph_2CH·OH]_0 = 2·21 \times 10^{-3}$M; $[H_2O]_{added} = 0·55$M.

H_2SO_4 (M)	k_2	− log I	H_2SO_4	k_2	− log I
0·633	$5·52 \times 10^{-4}$	3·88	1·588	$1·11 \times 10^{-2}$	2·56
1·149	$4·16 \times 10^{-3}$	3·00	1·774	$1·56 \times 10^{-1}$	2·40
1·381	$6·78 \times 10^{-3}$	2·74			

[*] The values now reported differ slightly from those reported earlier.[2] The cause of the discrepancy is uncertain. The new values were obtained under the same conditions as the other results in this paper, and should therefore be comparable with them.

p-*Dimethoxybenzene.*

(*A*) $[ArH]_0 = 1·62 \times 10^{-2}$M; $[Ph_2CH·OH]_0 = 1·63 \times 10^{-3}$M; $[H_2O]_{added} = 0·55$M.

1·241	$2·90 \times 10^{-3}$	2·89
1·390	$4·92 \times 10^{-3}$	2·74
1·490	$7·02 \times 10^{-3}$	2·65
1·639	$8·35 \times 10^{-3}$	2·52
1·738	$1·05 \times 10^{-2}$	2·43
1·986	$1·15 \times 10^{-2}$	2·23
2·235	$1·94 \times 10^{-2}$	2·02

(*B*) $[ArH]_0 = 1·47 \times 10^{-2}$M; $[Ph_2CH·OH]_0 = 1·29 \times 10^{-3}$M; $[H_2O]_{added} = 0·55$M.

1·176	$2·77 \times 10^{-3}$	2·97
1·306	$4·70 \times 10^{-3}$	2·82
1·428	$6·21 \times 10^{-3}$	2·70
1·734	$7·51 \times 10^{-3}$	2·43
1·897	$1·28 \times 10^{-2}$	2·30
2·070	$1·58 \times 10^{-2}$	2·16
2·475	$2·86 \times 10^{-2}$	1·82

o-*Dimethoxybenzene.*

(*A*) $[ArH]_0 = 9·34 \times 10^{-3}$M; $[Ph_2CH·OH]_0 = 7·94 \times 10^{-4}$M; $[H_2O]_{added} = 0·55$M.

0·993	$1·02 \times 10^{-2}$	3·20
1·092	$1·46 \times 10^{-2}$	3·06
1·390	$2·22 \times 10^{-2}$	2·74
1·492	$2·88 \times 10^{-2}$	2·65
1·589	$4·08 \times 10^{-2}$	2·56

(*B*) $[ArH]_0 = 9·31 \times 10^{-3}$M; $[Ph_2CH·OH]_0 = 9·48 \times 10^{-4}$M; $[H_2O]_{added} = 0·55$M.

0·476	$1·55_5 \times 10^{-3}$	4·25
0·641	$3·29 \times 10^{-3}$	3·85
0·864	$8·10 \times 10^{-3}$	3·42
1·097	$1·38 \times 10^{-2}$	3·06
1·103	$1·41 \times 10^{-2}$	3·04
1·180	$1·65 \times 10^{-2}$	2·96
1·289	$1·99 \times 10^{-2}$	2·83
1·659	$4·04 \times 10^{-2}$	2·50

m-*Dimethoxybenzene.*

(*A*) $[ArH_0] = 1·53 \times 10^{-2}$M; $[Ph_2CH·OH]_0 = 1·51 \times 10^{-3}$M; $[H_2O]_{added} = 0·55$M.

0·102	$2·81 \times 10^{-3}$	5·81
0·122	$4·29 \times 10^{-3}$	5·64
0·153	$5·09 \times 10^{-3}$	5·45
0·153	$5·96 \times 10^{-3}$	5·45
0·204	$9·83 \times 10^{-3}$	5·18
0·224	$1·29_5 \times 10^{-2}$	5·08
0·407	$4·51 \times 10^{-2}$	4·43

(*B*) $[Ph_2CH·OH]_0 = 1·99 \times 10^{-3}$M; $[H_2SO_4] = 0·107$M; $[H_2O]_{added} = 0$.

$10^2[ArH]_0$	2·08	4·15
10^3k_2	3·62	3·59

Benzene. $[ArH]_0 = 2·88 \times 10^{-1}$M; $[Ph_2CH·OH] = 1·456 \times 10^{-2}$M; $[H_2O]_{added} = 0·55$M.

H_2SO_4 (M)	k_2	− log I
3·75	$3·59 \times 10^{-6}$	0·96
3·89	$4·68 \times 10^{-6}$	0·86
4·89	$2·63 \times 10^{-5}$	0·19

anisole were purified by successive extractions with aqueous sodium hydroxide and water. The liquids were dried, finally by sodium, from which they were fractionally distilled.

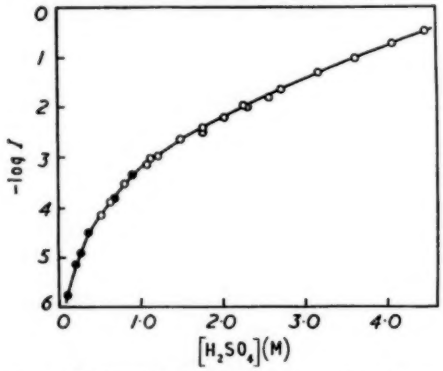
2,4- and 3,4-Dimethoxytriphenylmethane were made on a preparative scale by the method based on that used by Kundiger and Ovist [8] and described in Part I, starting from

[8] Kundiger and Ovist, *J. Amer. Chem. Soc.*, 1954, **76**, 2501.

diphenylmethanol and *m*- and *o*-dimethoxybenzene respectively (m. p.s of products 124° and 111—112°).

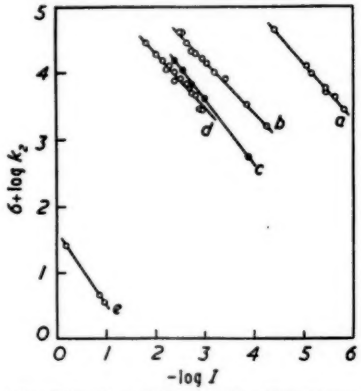
The interaction of diphenylmethanol and *p*-dimethoxybenzene is complicated by the formation of a disubstituted product under certain conditions, and was examined under two slightly differing sets of conditions. The reaction between diphenylmethanol (2·0 g.) and *p*-dimethoxybenzene (15 g.) in acetic acid (70—100 ml.) under the influence of sulphuric acid (10 ml., added dropwise, with vigorous shaking) gave, after 2½ hr., by usual methods of product separation, crude 2,5-dimethoxytriphenylmethane (3·0 g.; m. p. 97—99°, raised on recrystallisation from ethanol to 104—105°). The same reaction, when carried out with rapid addition of sulphuric acid or by the use of a higher ratio of *p*-dimethoxybenzene to diphenylmethanol, gave also a small amount of a white product, m. p. 207—208°, insoluble in ethanol. This material was the only product in the reaction of *p*-dimethoxybenzene with diphenylmethanol in the molar ratio 1 : 2 or on treatment of 2 : 5-dimethoxytriphenylmethane with diphenylmethanol in acetic acid–sulphuric acid. It was therefore considered to be a di-aralkylated dimethoxybenzene and, from the theory of aromatic substitution, therefore *1,4-bisdiphenylmethyl-2,5-dimethoxybenzene* [Found: C, 86·6; H, 6·6; OMe, 14·5%; *M* (Rast), 452. $C_{34}H_{30}O_2$ requires C, 86·8; H, 6·4; OMe, 13·2%; *M*, 470]. This compound was also formed as a by-product, in addition to 2 : 5-dimethoxytriphenylmethane, when the reaction between

FIG. 1. *Indicator ionisation in acetic acid-sulphuric acid containing water* (0·55 *mole l.*$^{-1}$).



○, 4-Methoxydiphenylmethanol; ●, 4,4′-dimethoxydiphenylmethanol [adjusted by equation (1)].

FIG. 2. *Relation between diphenylmethylation rates and indicator ionisation.*



(*a*) *m*-Dimethoxybenzene, (*b*) *o*-dimethoxybenzene, (*c*) anisole, (*d*) *p*-dimethoxybenzene, (*e*) benzene.

p-dimethoxybenzene (12 g.) and diphenylmethanol (2 g.) was carried out in benzene solution (50 ml.) in the presence of toluene-*p*-sulphonic acid.

Reaction velocities at 25° were measured spectrophotometrically, as previously described.[2] In every case the extrapolated values of the optical density for reaction mixtures at zero time and at the completion of the reaction agreed satisfactorily with values calculated on the basis of Beer's law from the previously determined spectra of the reactants and products in acetic acid.

In the experiments with benzene the solutions became turbid towards the end of the reaction owing to the precipitation of triphenylmethane. Timed samples were removed only during the earlier stages. To obtain " infinity " values in these experiments the whole of the suspension at the completion of the reaction was diluted with acetic acid so as to dissolve all the precipitate before the removal of portions for spectrophotometric examination.

The nature of the product (triphenylmethane) was in this case also established by the infrared spectrum of a sample of isolated product.

In all runs the concentration of benzene or methoxybenzene was greatly in excess (10- to 20-fold) of the concentration of diphenylmethanol, so that individual reactions followed a first-order course. The bimolecular nature of the reaction had been established earlier for anisole [2] and

has now been found again for the most reactive compound studied (*m*-dimethoxybenzene) by variation of that excess of concentration. Second-order rate constants, evaluated as before,[2] are in Table 1, the units being l. mole^{-1} sec.$^{-1}$ throughout.

Ionisation ratios of diarylmethanol indicators (4-methoxydiphenylmethanol, ROH, and 4,4′-dimethoxydiphenylmethanol, R′OH) were determined in this solvent system. In the short range of acidities in which measurements on both indicators were practicable, the two sets of ionisation ratios were related by the expression

$$\log \frac{[R^+]}{[ROH]_{stoich.} - [R^+]} = \log \frac{[R'^+]}{[R'OH]_{stoich.} - [R'^+]} - 3{\cdot}23 \quad . \quad . \quad . \quad (1)$$

the last term denoting the difference between the logarithms of the ionisation constants of the two indicators. The combined indicator results are summarised graphically in Fig. 1.

The kinetic and indicator results were again found to be related (Fig. 2) by the equation [2]

$$\log k_2 = \lambda \log I + \text{Constant}$$

where $I = \log \frac{[R^+]}{[ROH]_{stoich.} - [R^+]}$. Values of the slopes λ and of $\log k_2$ at selected values of I were also computed by the method of least squares and are given in Table 2.

TABLE 2. *Summary of results.*

Compound	λ	$\log I = 0$	$8 + \log k_2$ $\log I = -3$	$\log I = -6$
Benzene	$1{\cdot}12_1$	3·632	0·269	4·906
Anisole	$0{\cdot}97_9$	8·541	5·604	2·667
o-Dimethoxybenzene	$0{\cdot}79_7$	8·585	6·194	3·803
m-Dimethoxybenzene	$0{\cdot}87_4$	10·526	7·904	5·282
p-Dimethoxybenzene	$0{\cdot}84_8$	8·017	5·473	2·929
Mesitylene *	$0{\cdot}98_1$	8·005	5·062	2·119

* Kinetic results from ref. 2.

TABLE 3. *Relative reactivities in bromination and diphenylmethylation.*

Compound	Bromination [5]	Diphenylmethylation $I = 1$	$I = 10^{-3}$	$I = 10^{-6}$
Benzene	$8{\cdot}3 \times 10^{-10}$	$1{\cdot}2 \times 10^{-5}$	$4{\cdot}6 \times 10^{-6}$	$1{\cdot}7 \times 10^{-6}$
Anisole	(1)	(1)	(1)	(1)
o-Dimethoxybenzene	3·30	1·1	3·9	14
m-Dimethoxybenzene	$>10^4$	97	200	410
p-Dimethoxybenzene	0·075	0·3	0·74	1·8
Mesitylene	0·150	0·29	0·29	0·28

DISCUSSION

The experimental results show that the dependence of the alkylation velocity on acidity is not significantly altered when the reactivity of the aromatic compound is increased. The slopes obtained for the linear graphs of $\log k_2$ against H_0 are almost identical for the three dimethoxybenzenes, which span an approximately 100-fold range of reactivity. On the other hand, the slopes for anisole and mesitylene [2] are appreciably different, although the reactivities of these compounds are close to that of *p*-dimethoxybenzene. The difference is therefore not thought to arise from a difference in reaction mechanism but from a salting-out or " medium " effect of sulphuric acid, which is more or less constant for the isomeric dimethoxybenzenes but is different for anisole and mesitylene. The results obtained with benzene are not sufficiently detailed to warrant any conclusions in this respect.

The reaction velocity remains proportional to the concentration of aromatic compound ArH even for the most reactive compound investigated. This observation, taken in conjunction with the acidity dependence of the reaction velocity and earlier results,[2] indicates that the rate-controlling step of all the reactions studied is the bimolecular attack of the diphenylcarbonium ion upon ArH.

XUM

The measurements allow an estimate of the relative reactivities of benzene, anisole, mesitylene,[2] and the three dimethoxybenzenes towards diphenylcarbonium ions. This problem is also of some interest in view of seemingly conflicting evidence as to whether a methoxyl group activates or deactivates a *meta*-position.[5,9,10] Since the different lines in Fig. 2 are not exactly parallel, it is evident that the present study cannot provide a precise comparison of reactivities: the numerical values will depend on the solvent acidity chosen for making the comparison. In particular, there is an actual crossing over of the curves for anisole and *p*-dimethoxybenzene.

The lower values of the slopes for the dimethoxybenzenes cannot be attributed to basic behaviour of these compounds in the media investigated (in the sense of partial protonation of the compounds). Such behaviour would lead to a distinct curvature of the plots in Fig. 2. This point has also been directly examined in some detail for *m*-dimethoxybenzene. It was found that the ultraviolet absorption spectrum of *m*-dimethoxybenzene in acetic acid is identical with the spectrum immediately observed for this substance in the acidic media used in the kinetic experiments, and absence of any significant amount of protonation is therefore indicated. (A slow and irreversible reaction of unknown nature takes place in the acid solutions of *m*-dimethoxybenzene, but it makes no noticeable progress within the duration of the alkylation runs.)

Table 3 shows a comparison of the reactivities towards diphenylcarbonium ions of the different aromatic substrates studied at two different solvent acidities. The most direct comparison of our data is that with results on bromination in acetic acid [5] which have been included in the same Table. The different sets of results show the same general features, but the bromination velocities span a wider range of reactivities, *i.e.*, the effective brominating agent appears to be more discriminating than the diphenylcarbonium ion in its attack upon aromatic molecules.

It should be pointed out that the relative bromination reactivities quoted are also subject to some uncertainty. Since the different compounds studied [5] exhibit slightly different reaction orders with respect to bromine (at any rate those whose reaction orders have actually been established), the exact values of the relative reactivities depend upon the bromine concentration chosen for the comparison.

de la Mare and Vernon [5] used the bromination rates for benzene, anisole, and two dimethoxybenzenes to assess the effect of a methoxyl group at a position *meta* relative to it. This estimate was effectively based on the assumption that the effect of two methoxy-groups on another position in a dimethoxybenzene would be governed by independent additive contributions by each of the two groups towards the free energy of activation for substitution at that position. The conclusion reached on this basis was that a methoxyl group had a weakly activating effect at the *meta*-position. This conclusion is in contrast to the more recent direct experimental result that, for electrophilic hydrogen isotope exchange, a methoxyl group deactivates *meta*-positions.[9]

One can attempt to analyse the diphenylmethylation rates in the same manner as the bromination data. For example, by making use of diphenylmethylation velocities at (or extrapolated to) $\log I = -3{\cdot}0$ for benzene, anisole, and *o*- and *m*-dimethoxybenzene, one arrives at the conclusion that a methoxy-group activates *all* positions in an aromatic ring and that it causes the rate to increase *ca.* 100-fold at an *ortho*-position, *ca.* 2-fold at a *meta*-position, and *ca.* 10^6-fold at the *para*-position, in qualitative agreement with de la Mare and Vernon's conclusions. (At other acidities rather different partial rate factors would be obtained, and at very low values of $\log I$ the *meta*-position would apparently be deactivated.) However, if these figures are now used to calculate the reactivity of *p*-dimethoxybenzene, one obtains an answer which is about 10^3 times too small. Thus, the most significant conclusion to be drawn from the results is that the method of analysis is not self-consistent. A similar discrepancy cannot be detected in the bromination

[9] Satchell, *J.*, 1956, 3911.
[10] Okamoto and Brown, *J. Amer. Chem. Soc.*, 1957, **79**, 1909.

results, since the four rate constants available for the calculation provide just the requisite number of simultaneous equations to permit solution for the partial rate factors, but no more. However, the diphenylmethylation results indicate that any conclusions about substituent effects derived from the additivity principle must be treated with reserve.

The analysis can, of course, be made mathematically self-consistent by introducing one or more additional variables, *e.g.*, by assuming different values for the substituent effects exerted by vicinal methoxy-groups such as could be rationalised in terms of some kind of steric or electronic interaction between the neighbouring substituents. In view of the dependence of the relative reactivities on solvent acidity such further calculations do not seem justified. (A steric interpretation has, for instance, been put forward to explain the relative velocities of hydrolysis of 4- and 3 : 4-dimethoxybenzyl chloride.[11] These results suggest that, whereas a single 3-methoxy-group is expected to deactivate the side chain towards S_N1 substitution,[10] a 3-methoxy-group introduced into 4-methoxybenzyl chloride activates it. Here again, therefore, additivity of substituent effects is not observed.)

In connection with the failure of the additivity principle in diphenylmethylation, it should be recalled that many years ago Holleman drew attention [12] to its lack of success (*i.e.*, breakdown of the " product rule ") when applied to the further substitution of disubstituted benzenes in those cases where " the substituents already present endeavour to bring the new group to different places." The cases of *o*- and *p*-dimethoxybenzene fall into this category, and the failure of a treatment based on what is in effect the product rule would therefore perhaps not have been unexpected by Holleman.

KING'S COLLEGE, STRAND, LONDON, W.C.2. [*Received, August 20th*, 1958.]

[11] N. H. P. Smith, Discussion remarks in " Steric Effects in Conjugated Systems," Butterworths, London, 1958.
[12] Holleman, " Die direkte Einführung von Substituenten in den Benzolkern," Leipzig, 1910, pp. 480—488; *Chem. Rev.*, 1924, **1**, 187.

---

636. *The Tropylium Ion. Part V.*[1] *Synthesis of Cyclopropa*[l]*phenanthrene Derivatives and Attempted Formation of the Dibenzo*[a,c]*tropylium Cation.*

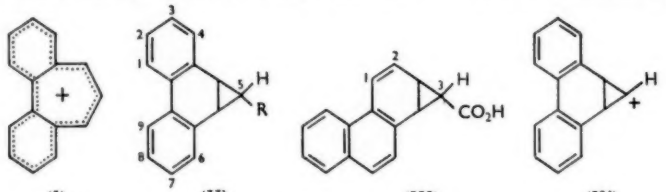
By M. J. S. DEWAR and C. R. GANELLIN.

With ethyl diazoacetate phenanthrene gives a 1,2-adduct in addition to the 9,10-adduct previously reported. The Hunsdiecker-reaction with the silver salt (II; R = CO_2Ag) gives the iodide (II; R = I), together with a monoester of 9-phenanthrylmethanediol. Curtius rearrangement of the azide (II; R = $CO{\cdot}N_3$), followed by hydrolysis, gives the amine which, on diazotisation in concentrated hydrochloric acid, furnishes the chloride. Attempts to prepare the dibenzo[*a,c*]tropylium cation indicate that this ion is less stable than predicted.

THE tropylium cation together with its benzologues provides a valuable opportunity for correlating experimental observation with predictions given by LCAO-MO theory. The pK values and the frequency of the first (long-wave) light-absorption bands of these cations have been calculated by Heilbronner and his collaborators.[2] Of this series, the 2,3-naphthotropylium and the dibenzo[*a,c*]tropylium (I) cation have not yet been prepared. The most promising route to the latter appeared to be by way of 5,5a-dihydro-4b*H*-cyclopropa[*l*]phenanthrene-5-carboxylic acid (dibenzonorcaradienecarboxylic acid) (II; R = CO_2H) which we hoped to convert into the cation (I) by one of the methods described in our previous publications.[1,3]

[1] Part IV, *J.*, 1959, 2438.
[2] Heilbronner, Meuche, and Strauss, *Helv. Chim. Acta*, 1958, **41**, 57, 414.
[3] Dewar and Pettit, *J.*, 1956, 2021, 2026.

The preparation of the acid (II; R = CO_2H) by the reaction of ethyl diazoacetate with phenanthrene was described by Drake and Sweeney [4] and confirmed by Cook, Dickson, and Loudon,[5] but neither group of investigators recorded the yield of purified product. On repeating this reaction we obtained a 50% yield of crude product, from which only a 6% yield of the desired acid (m. p. 256°) could be isolated. We also obtained an equal amount



(I) (II) (III) (IV)

of an isomeric acid (III) (m. p. 180°). The latter readily added one mol. of bromine and was easily oxidised by permanganate, indicating the presence of a localised ethylenic bond and excluding the possibility that phenanthrene had undergone substitution by ethyl diazoacetate to give a phenanthrylacetic ester. The light absorption of the acid (III) (Fig. 1) resembled that of α-vinylnaphthalene but showed extended conjugation. These results suggest that the acid was 3,3a-dihydro-2b*H*-cyclopropa[*a*]phenanthrene-3-carboxylic acid (III). Thus ethyl diazoacetate reacts with both the 9,10- and the 1,2-bond in phenanthrene and in this case cannot be considered as a selective " double-bond " reagent as defined by Badger.[6] Presumably reaction at the 3,4-bond is sterically hindered, and reaction is unfavourable at the 2,3-bond since this would produce an *ortho*-quinonoid structure.

Treatment of the silver salt of acid (I) with bromine, as in the normal Hunsdiecker reaction, did not produce the bromide (II; R = Br); instead, bromination of the phenanthrene nucleus occurred. A similar reaction with iodine was more successful but gave a mixture of the iodide (II; R = I) and an ester (A). Unfortunately, these could only be separated by a tedious fractional crystallisation and this limited their availability. Chromatography, on alumina or silica gel with a variety of solvents, was unsuccessful and chemical methods failed owing to the instability of their derivatives.

In contrast to tropylium iodide, the iodide (II; R = I) was readily soluble in organic solvents of low polarity and insoluble in aqueous acids, indicating that the covalent structure was dominant. It was not ionised even in 98% sulphuric acid, and addition of silver perchlorate to this solution resulted in oxidation. The iodide did react with silver perchlorate in dry nitromethane, producing silver iodide and a deep yellow solution; addition of dry ether to this solution removed the colour but failed to precipitate the expected dibenzotropylium salt, and evaporation gave a tar. These results indicated that dibenzotropylium perchlorate was formed in solution, giving rise to the observed yellow colour, but that it was too unstable to be isolated under these conditions.

The action of concentrated sulphuric acid on carboxylic acids R·CO_2H results in decomposition to R^+ if this is a stable ion; [7] *e.g.*, triphenylacetic acid gives carbon monoxide, water, and triphenylmethyl hydrogen sulphate. While the light absorption of the acid (II; R = CO_2H) in 98% sulphuric acid (Fig. 2) was very different from that in ethanol (Fig. 1), the expected long-wave band of the dibenzotropylium cation was absent and the acid rapidly underwent sulphonation.

Decarbonylation of the acid chloride (II; R = COCl) with silver perchlorate, in contrast to a similar reaction of cyclohepta-2,4,6-trienecarbonyl chloride,[1] did not lead to the desired cation but gave oxidation products.

[4] Drake and Sweeney, *J. Org. Chem.*, 1946, **11**, 67.
[5] Cook, Dickson, and Loudon, *J.*, 1947, 746.
[6] Badger, *Quart. Rev.*, 1951, **5**, 147.
[7] Gillespie and Leisten, *ibid.*, 1954, **8**, 40.

Since we had not been able to isolate a salt of the cation (I), we tried to prepare the alcohol (II; R = OH). This should rearrange in the presence of strong acids to the dibenzotropylium cation. The iodide (II; R = I) was easily hydrolysed; it gave a precipitate with silver nitrate in warm ethanol. Unfortunately, with sodium hydroxide it gave a mixture of acids. Attempts to convert the iodide into the acetate (II; R = OAc) failed. In a further attempt the acid (II; R = CO_2H) was converted, *via* the acid chloride, into the azide and then into the isocyanate (II; R = NCO) by a Curtius rearrangement. Acid-hydrolysis of the isocyanate gave the amine hydrochloride (II; R = NH_2,HCl). Diazotisation of this amine in dilute mineral acid gave polymeric material and none of the expected alcohol, and in concentrated hydrochloric acid the chloride (II; R = Cl) was produced. These results are very similar to those described by Pettit in the cyclopropa-acenaphthene series.[8]

The chloride (II; R = Cl), in contrast to the iodide, gave no reaction with alcoholic silver nitrate. The comparative ease with which the iodide was hydrolysed was therefore due to the weakness of the C–I bond and not to a tendency for the halide to ionise. Although the chloride appeared to be inert, when treated with aluminium chloride in

FIG. 1. *Ultraviolet spectra of the acid* (II; R = CO_2H) (——), *and* (III) (– – – –), *in ethanol.*

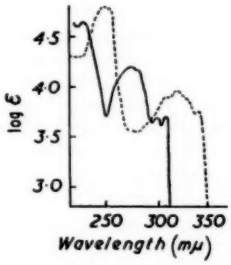
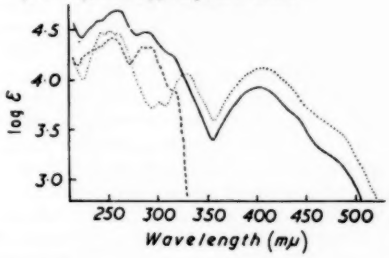


FIG. 2. *Ultraviolet spectra of the α-hydroxy-9-phenanthrylmethyl ester of the acid* (II; R = CO_2H) (——) *the acid* (II; R = CO_2H) (– – – –), *and phenanthrene-9-aldehyde* (. . . .), *in 98% sulphuric acid.*



nitromethane it gave a deep green solution, and addition of a trace of water destroyed the colour; however, the equivalent conductance of solutions of these two compounds in nitrobenzene did not indicate significant interaction. The chloride did not react with acetyl fluoroborate, antimony pentachloride, silver acetate, or silver perchlorate. These results are in contrast to the successful formation of the dibenzo[*a*,*e*]tropylium [9] and the perinaphthindenylium [8] cation from their corresponding covalent chlorides.

As already described, the Hunsdiecker reaction with iodine gave an ester (A) in addition to the expected iodide. A well-established product from this type of reaction is the ester between the starting acid and the next lower alcohol, *i.e.*, that formed by the Simonini reaction.[10] Hydrolysis of the ester (A) gave the acid (II; R = CO_2H), but the alcoholic constituent was not isolated. Esters, in general, undergo solvolysis in sulphuric acid, ionisation occurring with alkyl–oxygen fission:[11] $R'\cdot CO\cdot O\text{–}R + H_2SO_4 \longrightarrow R'\cdot CO_2H + R^+HSO_4^-$. The ester (A) dissolved in concentrated sulphuric acid with immediate production of a bright yellow colour and we assumed at first that this was due to the formation of the dibenzotropylium cation. However, dilution of this solution gave phenanthrene-9-aldehyde instead of the expected 2,3:4,5-dibenzocyclohepta-2,4,6-trienol (the base expected to be formed on hydrolysis of the cation). The aldehyde gave a yellow solution in 98% sulphuric acid and had a visible absorption identical with that of the

[8] Pettit, *Chem. and Ind.*, 1956, 1306.
[9] Berti, *Gazzetta*, 1957, **87**, 293.
[10] Johnson and Ingham, *Chem. Rev.*, 1956, **56**, 219.
[11] Kuhn, *J. Amer. Chem. Soc.*, 1949, **71**, 1575.

ester (A) (Fig. 2). Analysis of the ester (A) agreed with the formula (II; R = $CO{\cdot}O{\cdot}C_{15}H_{11}O$) and indicated that it was the half ester of 9-dihydroxymethylphenanthrene. It is likely that the carbonium ion (IV) is initially formed in the Hunsdiecker reaction and that this rearranges with autoxidation before esterification. A similar cationic intermediate has been demonstrated in the reaction of silver cyclobutanecarboxylate with iodine whereby cyclopropylmethyl cyclobutanecarboxylate is the major product.[12]

The difficulty encountered in preparing the dibenzo[*a*,*c*]tropylium cation indicates that it is less stable than predicted. The tribenzo[*a*,*c*,*e*]tropylium cation [13] is also much less stable than predicted and a common feature of these two cations is the resistance to planarity of the seven-membered ring, and therefore to effective overlap of adjacent *p*-orbitals, arising from steric interference of the *o*-hydrogen atoms; the LCAO-MO calculations neglect the effect of configurational interaction. The failure to prepare the alcohol (II; R = OH) in the above experiments suggests that this too is unstable.

Experimental

Microanalyses were carried out by the microanalytical laboratory of the Imperial College of Science and Technology, London. Ultraviolet absorption spectra were determined with a Unicam S.P. 500 spectrophotometer.

Addition of Ethyl Diazoacetate to Phenanthrene.—Ethyl diazoacetate (180 g.) was added dropwise with stirring to liquid phenanthrene (1040 g.) at 155—165°. The addition was controlled to give a steady evolution of nitrogen and required 6 hr. Heating was continued for a further 1 hr. and *ca.* 34 l. of nitrogen were collected. The hot mixture was then refluxed with potassium hydroxide (90 g.) in ethanol (3 l.) for 3½ hr. and poured into water (6 l.); the precipitated phenanthrene was filtered off from the cold solution and washed with 2N-sodium hydroxide (200 ml.). The washings were combined with the main filtrate, then extracted with ether (2 × 500 ml.) to remove traces of phenanthrene and evaporated under reduced pressure to half the volume. Acidification of this solution with concentrated hydrochloric acid gave the product as a sticky precipitate which became granular after a few hours and was then filtered off and dried (yield, 185 g., 50%).

The crude acid was stirred with boiling benzene (400 ml.) and the mixture was filtered while hot. The residue was fractionally crystallised (" triangular method ") from dioxan and gave the acid (II; R = CO_2H) as needles (22 g., 5·9%), m. p. 255—256·5° (Found: C, 81·5; H, 5·3. Calc. for $C_{16}H_{12}O_2$: C, 81·3; H, 5·1%)

Partial evaporation of the benzene filtrate afforded a solid which was recrystallised several times from benzene, to give 3,3a-*dihydro*-2bH-*cyclopropa*[a]*phenanthrene*-3-*carboxylic acid* as prisms (23·5 g., 6·3%), m. p. 180—181° [Found: C, 81·7; H, 5·4%; equiv., 239; *M* (Rast), 236. $C_{16}H_{12}O_2$ requires C, 81·3; H, 5·1%; equiv., and *M*, 236]. A solution of this acid in benzene readily reacted with bromine to give a pale yellow solid which could not be crystallised since in warm benzene hydrogen bromide was evolved and a yellow resin remained.

Similar results were obtained on addition of ethyl diazoacetate under the conditions described by Drake and Sweeney,[4] *viz.*, at a lower temperature, with a lower concentration of ethyl diazoacetate, and for a longer time.

Hunsdiecker Reaction.—The acid (II; R = CO_2H) was neutralised with warm 0·2N-sodium hydroxide, and an equivalent amount of aqueous silver nitrate was added. The white precipitate of the silver salt was filtered off and washed with water, then acetone, partially dried at 100° for 30 min., and finally dried *in vacuo* over phosphoric oxide (yield 97%).

(*a*) Bromine (3·1 g., 0·0194 mole) was added dropwise with stirring to a suspension of the silver salt (6·7 g., 0·0196 mole) in dry, refluxing carbon tetrachloride (750 ml.). No carbon dioxide was evolved. Refluxing was continued for 2½ hr. The mixture was filtered from the precipitate of silver bromide, extracted with 2N-sodium hydroxide (2 × 70 ml.) and evaporated, leaving a polymeric residue. The alkaline extracts, together with some sodium salt which had been precipitated, were acidified and the resulting precipitate was filtered off, dried, and crystallised from benzene to give white needles of x-*bromo*-5,5a-*dihydro*-4bH-*cyclopropa*[l]*phenanthrene*-5-*carboxylic acid* (3·5 g., 58%), m. p. 271—273° (decomp. 274°) (Found:

[12] Roberts and Simmons, *J. Amer. Chem. Soc.*, 1951, **73**, 5487.
[13] Stiles and Libbey, *J. Org. Chem.*, 1957, **22**, 1243.

C, 60·8; H, 3·8; Br, 24·9. $C_{16}H_{11}O_2Br$ requires C, 61·0; H, 3·5; Br, 25·4%), $\lambda_{max.}$ (in ethanol) 224, 276—282, 307, 315 mμ (log ε 4·62, 4·20, 3·89, 3·87 respectively).

(*b*) The silver salt (19·1 g., 0·056 mole) was added to a solution of resublimed iodine (14·2 g., 0·056 mole) in dry benzene (900 ml.) at 0°; the mixture was stirred for 1½ hr. at 0°, then refluxed for 2½ hr. during which carbon dioxide was evolved. The precipitated silver iodide was then filtered off and dried (12·8 g., 98%). The benzene filtrate was extracted with 2N-sodium hydroxide (2 × 100 ml.), and these extracts together with some sodium salt which had been precipitated were acidified to give the acid (II; R = CO_2H) (4·2 g., 32%). Evaporation of the benzene solution gave two products (8·3 g.) in nearly equal amounts which were separated by fractional crystallisation from benzene. *5,5a-Dihydro-5-iodo-4bH-cyclopropa*[l]*phenanthrene*, which was the less soluble, crystallised as pale yellow prisms, m. p. 140° (decomp.) (Found: C, 56·4; H, 3·6; I, 40·6. $C_{15}H_{11}I$ requires C, 56·6; H, 3·5; I, 39·9%), $\lambda_{max.}$ (in chloroform) 256—268 mμ (log ε 4·05). The other component, which crystallised as needles, was *α-hydroxy-9-phenanthrylmethyl 5,5a-dihydro-4bH-cyclopropa*[l]*phenanthrene-5-carboxylate*, m. p. 238—239° (Found: C, 84·2; H, 5·0. $C_{31}H_{22}O_3$ requires C, 84·0; H, 5·0%), $\lambda_{max.}$ (in chloroform) 256, 268—271 (infl.), 274—277 (infl.), 298, 309·5, 330, 337, 345 mμ (log ε 4·67, 4·41, 4·39, 4·15, 3·87, 2·30, 2·14, 2·06 respectively).

Hydrolysis of the ester (140 mg.) by refluxing benzene (20 ml.) and 4N-sulphuric acid (30 ml.) for 2 hr. gave the acid (II; R = CO_2H) (77 mg.), identified by its ultraviolet light absorption and mixed m. p.

Treatment of the ester (110 mg.) for 5 min. with 98% sulphuric acid (2 ml.) gave a deep yellow solution. This was poured on ice (20 g.), and the precipitate was filtered off and washed with warm 2N-sodium hydroxide. Crystallisation of the residue from light petroleum (b. p. 60—80°) gave 9-phenanthrenealdehyde (10 mg.), m. p. 100—101°, having ultraviolet and infrared spectra identical with those of material prepared by Dornfeld and Coleman's method.[14]

Silver perchlorate (0·20 g.) in dry nitromethane (2 ml.) was added to a solution of the iodide (0·17 g.) in dry toluene (3 ml.), and the mixture was heated at 80° for 5 min. in nitrogen. The resulting precipitate of silver iodide was filtered off under nitrogen, and dry ether (from sodium) was added to the deep yellow filtrate. Although the colour had been destroyed no salt was precipitated; evaporation gave a green polymer. The effect of traces of moisture rendered it impossible to measure the light absorption of the above yellow filtrate.

Treatment of the Acid (II; R = CO_2H) *with Sulphuric Acid.*—The acid (0·41 g.) with 98% sulphuric acid (3 ml.) gave a green solution. After 10 min. this was poured on ice (10 g.), and the precipitate was filtered off. Crystallisation from benzene containing a few drops of ethanol gave needles, m. p. 157—159° (decomp.). This product was very hygroscopic and gave an acidic solution in water; it contained sulphur but did not give consistent analyses. In ethanol it had $\lambda_{max.}$ 228, 276, 286, 301, 313 mμ (log ε 4·41, 4·16, 4·16, 3·80, 3·79 respectively).

5,5a-Dihydro-4bH-cyclopenta[l]*phenanthrene-5-carboxylic Anhydride.*—When the acid chloride (II; R = COCl) (see below) was treated with pyridine, as in the procedure of Allen *et al.*[15] for *p*-chlorobenzoic anhydride, the *anhydride* was obtained; it crystallised from benzene as needles, m. p. 233—234° (90%) (Found: C, 84·5; H, 5·2. $C_{32}H_{22}O_3$ requires: C, 84·7; H, 4·9%), $\lambda_{max.}$ (in chloroform) 251, 272, 281, 297, 310 mμ (log ε 4·68, 4·52, 4·51, 4·15, 4·08 respectively).

Curtius Reaction.—The acid (II; R = CO_2H) (15 g.) was refluxed for 1½ hr. with thionyl chloride (10 g.) in benzene (100 ml.) containing 6 drops of pyridine. The solution was decanted from pyridine hydrochloride and evaporated. The residue of acid chloride crystallised from light petroleum (b. p. 80—100°) (charcoal) as needles (14·3 g., 89%), m. p. 151°.

To a suspension of the acid chloride (14·2 g.) in acetone (150 ml.) at 0°, sodium azide (5·4 g., 50% excess) in water (13 ml.) was added dropwise with stirring. After being stirred for a further 20 min. the mixture was treated with water (200 ml.) and extracted into benzene (250 ml.). The benzene solution was washed with water (3 × 200 ml.), then dried (Na_2SO_4), and 50 ml. of the benzene were distilled off under reduced pressure. The solution was restored to 250 ml. by the addition of dry benzene and then refluxed gently for 3½ hr., by which time the evolution of nitrogen had ceased. Evaporation of the solution afforded the isocyanate (II; R = CNO), m. p. 78° [from benzene–light petroleum (b. p. 60—80°)].

The isocyanate was refluxed with stirring with concentrated hydrochloric acid (150 ml.) for 1 hr. On cooling, the *amine* (II; R = NH_2) *hydrochloride* separated. It crystallised from

[14] Dornfeld and Coleman, *Org. Synth.*, Coll. Vol. III, 1955, p. 701.
[15] Allen, Kibler, McLachlin, and Wilson, *ibid.*, p. 28.

XUM

dilute hydrochloric acid as plates (9·8 g., 72%), m. p. 244° (Found: C, 73·7; H, 6·0; N, 5·5; Cl, 14·5. $C_{15}H_{14}NCl$ requires C, 73·9; H, 5·8; N, 5·7; Cl, 14·6%). Liberation of the base gave a white solid which readily became yellow in air.

Diazotisation.—(a) *In dilute acid.* Sodium nitrite (0·7 g., 100% excess) in water (10 ml.) was added dropwise during 30 min. with stirring to the amine hydrochloride (1·5 g.) in 2N-hydrochloric acid (20 ml.) and ether (30 ml.) at −5°. The mixture was stirred for 30 min. at 18°, then warmed at 30—35° for 30 min. The ether layer was washed with 2N-ammonia, then water, and dried (Na_2SO_4). Evaporation of the ether gave a yellow resin.

(b) *In concentrated acid.* The amine hydrochloride (5·0 g.) was dissolved in concentrated hydrochloric acid (140 ml.), acetic acid (20 ml.), and ether (100 ml.). Sodium nitrite (2·5 g., 100% excess) in water (10 ml.) was added dropwise during 45 min. to the stirred mixture at 0°. The mixture was then stirred for 1 hr. at 18°, water (250 ml.) was then added, and the ether layer was separated off. The ethereal solution was washed well with 2N-ammonia, then water, dried (Na_2SO_4), and evaporated to yield red crystals. These were chromatographed in the minimum quantity of benzene on alumina, with 1 : 1 benzene–light petroleum (b. p. 60—80°) as eluant, to give the *chloride* (II; R = Cl) (1·8 g., 40%), needles, m. p. 90·5—91° (from ethanol) (Found: C, 79·6; H, 5·2; Cl, 15·5. $C_{15}H_{11}Cl$ requires C, 79·5; H, 4·9; Cl, 15·6%), $\lambda_{max.}$ (in ethanol) 218—222, 238, 246, 276, 283—287 (infl.), 300, 312 mμ (log ε 4·63, 4·29, 4·27, 4·06, 3·99, 3·62, 3·65 respectively).

We thank the D.S.I.R. for a maintenance grant (to C. R. G.) and the University of London for a grant for spectroscopic equipment.

QUEEN MARY COLLEGE (UNIVERSITY OF LONDON),
MILE END ROAD, LONDON, E.1. [*Received, March 25th,* 1959.

---

637. 1,2:3,4:5,6:7,8:9,10:11,12-*Hexabenzotriphenylene.*

By JOHN G. CAREY and IAN T. MILLAR.

Reaction of 9,10-dichlorophenanthrene with magnesium in boiling tetrahydrofuran gives 1,2:3,4:5,6:7,8:9,10:11,12-hexabenzotriphenylene.

THE reactions of several *ortho*-dihalogenated benzenoid compounds with magnesium and lithium have recently been described:[1,2,3] it has been suggested that the polycyclic hydrocarbons produced in these reactions arise through the formation of benzyne-type intermediates. We now record a brief investigation of the reaction of 9,10-dichlorophenanthrene with these metals.

(I)

9,10-Dichlorophenanthrene was prepared by uncatalysed chlorination of phenanthrene,[4] a reaction which contrasts with the uncatalysed bromination of this hydrocarbon[5] in that only the former gives the 9,10-dihalogenated product in fair yield. 9,10-Dichlorophenanthrene was found to react only very slowly with lithium or magnesium in diethyl ether; however, it reacts with magnesium in boiling tetrahydrofuran, to give a crude neutral product from which a colourless hydrocarbon, m. p. 380°, was isolated by chromatography and fractional precipitation.

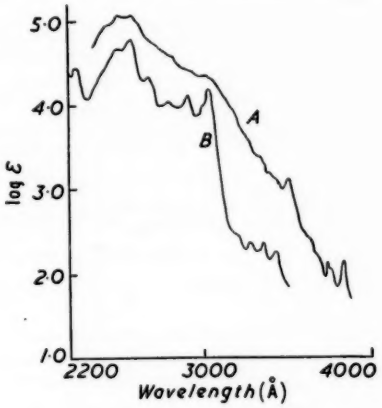
This is formulated as 1,2:3,4:5,6:7,8:9,10:11,12-hexabenzotriphenylene (I) on the basis of analysis and molecular-weight determination, mode of formation, and ultraviolet absorption (see Figure).

The ultraviolet absorption spectrum of 9,9′-biphenanthryl is described[6] as practically identical with that of phenanthrene, presumably as the result of steric prevention of

[1] Millar and Heaney, *Quart. Rev.*, 1957, **11**, 109.
[2] Heaney, Mann, and Millar, *J.*, 1957, 3930.
[3] Hinton, Mann, and Millar, *J.*, 1958, 4704.
[4] Sandqvist and Hagelin, *Ber.*, 1918, **51**, 1515.
[5] Henstock, *J.*, 1921, **119**, 55; 1923, **123**, 3097.
[6] Henri and Bergmann, *Nature*, 1939, **143**, 278.

planarity and the resulting inhibition of conjugative interaction between the phenanthryl systems. It follows that the absorption of 9,10-di-9′-phenanthrylphenanthrene, which would give analytical values similar to those of the hydrocarbon (I), should be closely similar to that of phenanthrene, since steric inhibition of interaction between the phenanthryl systems would clearly be considerable; this compound would be expected to show $\log_{10} \varepsilon \sim 5{\cdot}3$ for the principal absorption maximum.

1,2:3,4:5,6:7,8:9,10:11,12-Hexabenzotriphenylene may be formed in this reaction by a route analogous to those postulated, for example, as possibly responsible for the formation of triphenylene in the reaction of *o*-bromoiodobenzene with lithium,[2] and of



Ultraviolet absorption maxima (Å) *and* log ε (*in parentheses*) *of*: (*A*) 1,2:3,4:5,6:7,8:9,10:11,12-*hexabenzotriphenylene in* 1,4-*dioxan*, 2500 (5·08), 2580 (5·07), 3030 (4·35), 3520 (3·12), 3750 (2·14), 3850 (2·14); *and* (*B*) 9,10-*dichlorophenanthrene in* 95% *ethanol*, 2250 (4·45), 2570 (4·79), 2680 (4·34), 2810 4·05), 2920 (4·12), 3040 (4·18), 3280 (2·36), 3360 (2·36), 3440 (2·26).

2,6,11-trimethyltriphenylene in the reaction of 3-bromo-4-iodotoluene with lithium.[3] Such a route would involve the formation, and subsequent addition reactions, of a phenanthryne intermediate.

It is noteworthy that the hydrocarbon (I) cannot be planar, as a result of steric conflict at the 1-positions of the phenanthrylene units; the deviation from planarity may be comparable with that shown by 3,4:5,6-dibenzophenanthrene, which has been examined by *X*-ray crystal analysis.[7]

Experimental

9,10-*Dichlorophenanthrene*.—Dry chlorine was passed into phenanthrene (100 g.) in carbon tetrachloride (200 ml.) at 0—5° until absorption became slow (*ca.* 80 g. during 3·5 hr.). The solvent was then removed, and the residue (which solidified at room temperature) distilled, giving the dichloro-compound, b. p. 175—185°/0·1 mm. (70—80 g., 50—60%): recrystallised from benzene, acetic acid, and ethanol, it formed colourless needles, m. p. 160·5° (lit.,[4] m. p. 160—160·5°) (Found: C, 68·1; H, 3·35. Calc. for $C_{14}H_8Cl_2$: C, 68·05; H, 3·25%). A sample oxidised with chromic anhydride and sulphuric acid in acetic acid gave 9,10-phenanthraquinone, m. p. and mixed m. p. 203°. The ultraviolet absorption spectrum of the dichlorophenanthrene is given in the Figure.

1,2:3,4:5,6:7,8:9,10:11,12-*Hexabenzotriphenylene*.—9,10-Dichlorophenanthrene (5·5 g.) in tetrahydrofuran (250 ml.) was added to magnesium (1·2 g., 2 equivs.), activated by heating with iodine or by the addition of a few drops of ethyl bromide, and the whole was stirred and boiled under reflux in a nitrogen atmosphere. After an induction period of 2—3 hr. the initially pale yellow solution became dark green as the magnesium dissolved. After being boiled under reflux for a further 2 hr., and then stirred at room temperature for 1 hr., the mixture was decanted from excess of magnesium, and the solvent was removed. Magnesium chloride was extracted from the residue by water, and the dried residue chromatographed in benzene on alumina; 9,10-dichlorophenanthrene was preferentially retained on the column. Evaporation

[7] McIntosh, Robertson, and Vand, *J.*, 1954, 1661.

XUM

of the eluate gave the *hydrocarbon* (2·35 g., 60%), which after recrystallisation from benzene or xylene and fractional precipitation from its benzene solution by ethanol, formed a colourless powder, m. p. 380° (Found: C, 94·9; H, 5·05%. *M*, cryoscopic in phenanthrene, 558. $C_{42}H_{24}$ requires C, 95·4; H, 4·6%; *M*, 527). In a similar experiment, the mixture was carboxylated; working-up in the usual manner gave the above hydrocarbon, together with traces only of an acidic product which was not investigated.

Solutions of the hydrocarbon in benzene failed to deposit a picrate with picric acid in ethanol. The hydrocarbon was insoluble in cold concentrated sulphuric acid. In benzene or 1,4-dioxan it showed a blue fluorescence. In solid solution in 1,4-dioxan cooled in liquid nitrogen, the hydrocarbon showed a pale green phosphorescence after irradiation with high-intensity ultraviolet light.[8]

We are indebted to Dr. P. H. Plesch and Dr. T. E. Peacock for helpful discussions, and to the Department of Scientific and Industrial Research for a grant (to J. G. C.).

UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE,
KEELE, STAFFORDSHIRE.

[*Received, April 22nd,* 1959.]

[8] Clar, Ironside, and Zander, *J.*, 1959, 142.

---

638. *Studies in Relation to Biosynthesis. Part XX.* The Structure and Biosynthesis of Curvularin.*

By A. J. BIRCH, O. C. MUSGRAVE, R. W. RICKARDS, and HERCHEL SMITH.

The mould metabolite, curvularin, has been shown to be a lactone (VI; R = H) containing a twelve-membered ring. Its biosynthesis involves the head-to-tail linkage of eight acetic acid units.

PRELIMINARY work[1,2] indicated the partial structure (I; $R^1 = R^2 = H$, $R^3 = O$) for curvularin, $C_{16}H_{20}O_5$, a metabolite of a *Curvularia* species [F334 in the Nobel Division Collection (Imperial Chemical Industries Limited); Commonwealth Mycological Institute Cat. No. I.M.I. 52,980]. We present here evidence defining the structure and the biosynthetic units involved.

Structure.—The structural work can be resolved into determination of the number of *C*-Me groups, definition of the unknown oxygen functions, and their location.

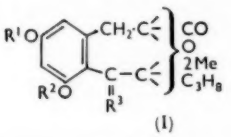
The original assignment of 2 *C*-Me groups rested on the production of *ca.* 1·5 mols. of acetic acid on Kuhn–Roth oxidation. In our hands this oxidation gave 1·05 and 0·89 mol. in replicate determinations, indicating that curvularin may have only one *C*-Me group. We reached a decision in a novel way. The partial structure (I) suggested biosynthesis, at least in part, from acetic acid units: in particular, formation of the acylresorcinol fragment could be envisaged as involving cyclisation of an intermediate of partial structure (II) containing a carbon chain formed by serial head-to-tail linkage of acetic acid units.[3] We found that the mould incorporated radioactivity from $Me\cdot{}^{14}CO_2H$ into curvularin to the extent of *ca.* 4% and that the acetic acid produced by Kuhn–Roth oxidation contained approximately one-eighth of the total activity, all of it on the carboxyl group. We can therefore infer that the C_{16} metabolite is derived from eight acetic acid units very probably incorporated through a straight-chain precursor, a conclusion later supported by examination of other degradations set out below. It therefore contains one *C*-Me group which is presumably associated with the acetic acid unit at one end of the chain. We believed that the presence of 2 *C*-Me groups would have implied a biosynthesis from eight acetic acid units (one of them decarboxylated), with the

* Part XIX, Birch, Ryan, and Smith, *J.*, 1958, 4773.

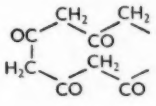
[1] Musgrave, *J.*, 1956, 4301.
[2] *Idem*, *J.*, 1957, 1104.
[3] Cf. Birch, Massy-Westropp, and Moye, *Austral. J. Chem.*, 1958, **8**, 539; Birch, Massy-Westropp, Rickards, and Smith. *Proc. Chem. Soc.*, 1957, 98; *J.*, 1958, 360.

introduction of a second methyl group on to a carbon atom in the skeleton derived from the methyl-carbon of acetic acid *e.g.*, as in the expression (III).[4] Kuhn–Roth oxidation of the labelled metabolite would then have resulted in dilution of the active acetic acid from the end acetate unit with inactive acid produced from the methylated position, and the resulting acetic acid would have contained a smaller fraction of the total activity than that found (one-fourteenth of the total if each *C*-Me had contributed equally to the Kuhn–Roth acid). Transmethylations on to carbon [4,5] have been diagnosed in a number of biological systems by location of the radioactivity from $H\cdot{}^{14}CO_2H$ or [$^{14}CH_3$]methionine on the, introduced groups. With curvularin radioactivity from $H\cdot{}^{14}CO_2H$ was incorporated, but only to a very small extent and with general distribution throughout the molecule. The absence of transmethylation in the biosynthesis and therefore of a second methyl group in the metabolite is thus confirmed. It is notable that in the acetic acid obtained by Kuhn–Roth oxidation of $H\cdot CO_2H$-derived curvularin the ratio of the labelling on the methyl- and the carboxyl-carbon atoms is approximately **5 : 1.**

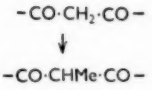
We turn next to the definition of the five oxygen functions. Musgrave [1,2] had proved that two oxygen atoms are associated with phenolic hydroxyl groups and had obtained spectroscopic evidence that two more are associated with carbonyl groups, one of which is ketonic and conjugated with the aromatic nucleus. The nature of the second carbonyl group and of the remaining oxygen atom remained undecided. We confirmed the presence of a ketonic group by formation of a monoxime and located the remaining two oxygen atoms in a lactone group by the following evidence. Curvularin contains no olefinic unsaturation [1] and from the molecular formula must contain at least one ring in addition to the aromatic nucleus. The infrared absorption spectra of curvularin and its dimethyl ether (I; $R^1 = R^2 = Me$, $R^3 = O$) are consistent with the presence of a lactone group, and both substances react with aqueous alkali but fail to give a positive reaction in the hydroxamic acid test for the carboxylic ester group.[1,2] With warm aqueous potassium hydroxide *in vacuo* curvularin gave an amorphous product which rapidly darkened in alkaline solution in air. Under parallel conditions, but in aqueous-methanolic potassium hydroxide, curvularin dimethyl ether gave an isomer, $C_{18}H_{24}O_5$, containing an acylatable alcoholic hydroxyl group but lacking the carboxyl group expected from hydrolysis of a lactone. We return to the structure of this substance below. By the same treatment, deoxydihydromonomethylcurvularin (I; $R^1 =$ H or Me, $R^2 =$ Me or H, $R^3 = H_2$), formed from deoxydihydrocurvularin [2] (I; $R^1 = R^2 =$ H, $R^3 = H_2$) by treatment with an excess of ethereal diazomethane, gave a hydroxy-carboxylic acid, $C_{17}H_{26}O_5$, revealing the lactone group in this substance and hence in curvularin. Curvularin thus contains an oxo-lactone ring fused in the 4,5-position to a resorcinol nucleus.



(I)



(II)



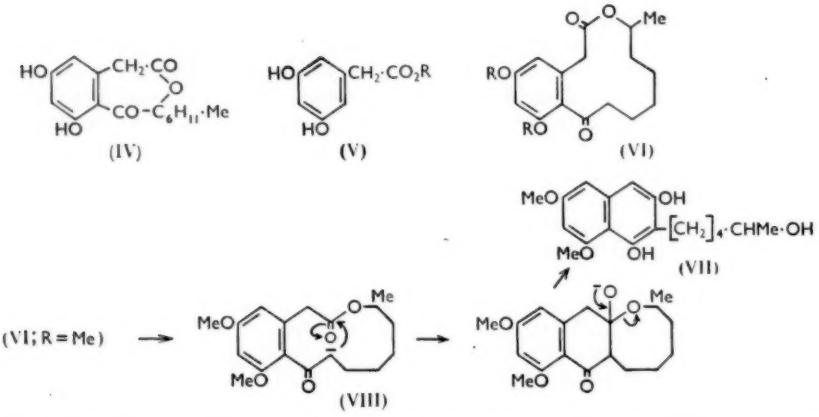
(III)

Refluxing curvularin with red phosphorus and hydriodic acid in acetic acid gave a neutral product and an acidic fraction containing an alkanoic and an iodoalkanoic acid which were soluble in aqueous sodium hydrogen carbonate and sodium carbonate respectively. The alkanoic acid was identified as octanoic acid by its paper-chromatographic behaviour and infrared spectrum. The iodo-acid was shown to be an iodo-octanoic acid by reduction with Raney alloy and sodium hydroxide [6] to octanoic acid. The neutral fraction had infrared bands at 1780 and 1181 cm.$^{-1}$, suggesting the presence of a γ-lactone.

[4] Cf. Birch, Fitton, Pride, Ryan, Smith, and Whalley, *J.*, 1958, 4576.
[5] Alexander and Schwenk, *J. Amer. Chem. Soc.*, 1957, **79**, 4554; Alexander, Gold, and Schwenk, *J. Biol. Chem.*, 1958, **232**, 599.
[6] Schwenk, Papa, Whitman, and Ginsberg, *J. Org. Chem.*, 1944, **9**, 1.

XUM

Controlled oxidation by chromic acid [7] gave acetic, propionic, butyric, and succinic acid. Fusion with potassium hydroxide gave propionic, valeric, and a trace of acetic acid. The formation of succinic acid by oxidation and valeric acid by alkali fusion, together with the occurrence of octanoic acids as fission products, strongly suggests that the neutral product is the lactone of 4-hydroxyoctanoic acid. The formation of octanoic acid derivatives is most readily interpreted as due to acid-hydrolysis of a 4-acylresorcinol system; the partial structure may accordingly be expanded to (IV). This interpretation was supported by fission under non-reducing conditions with hydrobromic acid in acetic acid. The products included a bromo-acid, converted by reductive dehalogenation into octanoic acid, the above-mentioned lactone, and a phenolic carboxylic acid. The phenolic acid was difficult to purify and was converted into its methyl ester which was identified as methyl 3,5-dihydroxyphenylacetate [8] (V; R = Me). It is notable that the isolation of two C_8 fragments of apparently mutually exclusive structures accounts for all of the carbon atoms of curvularin. Together with the formation of 2-carboxymethyl-4,6-dimethoxyphenylglyoxylic acid on oxidation of dimethyl curvularin by alkaline permananate, these results prove the carbon skeleton of structure (IV) to be correct. The structural feature still undefined is the point of lactonisation on the octanoyl chain. No significance can be attached to the formation of a γ-lactone since the forcing conditions used would be expected to give the most stable lactone from the halogeno-, hydroxy-, or acetoxy-octanoic acid produced in the initial fission. The location of the lactonic-oxygen atom at the 7-position of the chain follows from the formation of acetic acid as the only steam-volatile acid by controlled oxidation of curvularin by chromic acid,[7] and of iodoform and pimelic acid on oxidation of an alkaline solution of curvularin with hydrogen peroxide and treatment of the product with sodium hypoiodite. Curvularin accordingly has structure (VI; R = H).

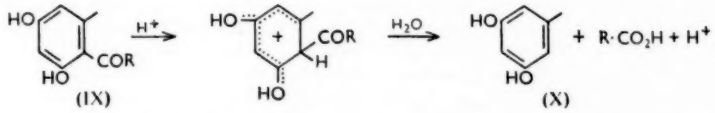


This structure is consistent with the spectral and chemical properties. The ultraviolet and infrared absorption of curvularin indicate a lower degree of conjugation of the carbonyl group with the aromatic nucleus than is observed with the analogous 2,4-dihydroxy-6-methylacetophenone, presumably because of non-coplanarity.[2] In 2,4-dihydroxy-6-methylacetophenone coplanarity is attributed to hydrogen-bonding between the carbonyl and the 2-hydroxyl group which apparently outweighs the tendency of the *o*-alkyl group to force the carbonyl group out of the plane of the aromatic nucleus (for a discussion see ref. 2). In curvularin the same two effects may operate but coplanarity is probably resisted by the high energy of the requisite conformations of the macrocycle. Leonard and

[7] Garbers, Schmid, and Karrer, *Helv. Chim. Acta*, 1954, **37**, 1336.
[8] Theilacher and Schmid, *Annalen*, 1950, **570**, 18.

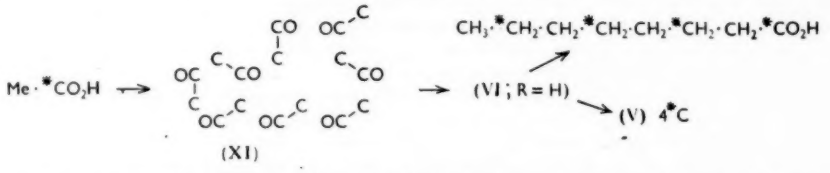
Owens [9] have recently shown, chemically and spectroscopically, the resistance to coplanarity of the C=C–C=O system in cyclododec-2-enone.

The nature of the isomer $C_{18}H_{24}O_5$ obtained from di-*O*-methylcurvularin with methanolic alkali follows directly from the structure (VI; R = Me). The infrared spectrum indicates only phenolic and alcoholic hydroxyl groups; the ultraviolet absorption is reminiscent of a hydroxynaphthalene system, and the compound is reasonably formulated as the naphthol (VII) produced by the transannular Claisen-condensation represented by the sequence (VI; R = Me) ⟶ (VIII) ⟶ (VII). With ethereal diazomethane this naphthol afforded only a trimethoxynaphthalene and it resisted complete esterification with acetic anhydride; this we attribute to the low reactivity of the *peri*-hydroxyl group. The formation of naphthols of type (VII) explains the failure of the hydroxamic acid test for the carboxylic ester group on curvularin and di-*O*-methylcurvularin.



Removal of the acyl side chain under strongly acid conditions may plausibly be regarded as the reverse of a Friedel–Crafts acylation, in which the initial protonation in the sequence (IX) ⟶ (X) would be facilitated by delocalisation of the positive charge on the hydroxylic oxygen atoms. This reaction is apparently analogous to the formation of resorcinol (as shown by production of fluorescein) from 2,4-dihydroxyacetophenone by sulphuric acid.[10]

Biosynthesis.—Evidence for biosynthesis involving head-to-tail linkage of eight acetate units is given above. Confirmation is provided by the fission of the labelled curvularin by hydrogen bromide. The two C_8 fragments obtained from this reaction, each representing four intact acetate units, contained, as required, equal amounts of radioactivity which together accounted for the total. The biosynthesis may be represented as (XI) ⟶ (VI; R = H). Curvularin is the first example of a naturally occurring macrocyclic



lactone having a methyl group as the only alkyl substituent, and constitutes an interesting structural (and possibly biosynthetic) link between the macrolide antibiotics [11] (*e.g.*, methymycin [11b]) and the acetate-derived phenols.[12] The remarkable ease of the transannular cyclisation, giving the naphthol (VII), prompts the speculation that macrocyclic lactones may in some cases be intermediates in the production of polycyclic aromatic acetate-derived compounds.

Experimental

Ultraviolet spectra were taken in ethanol. Light petroleum was of b. p. 40—60°. Carboxylic acids were chromatographed as the ammonium salts, by ascending development on Whatman No. 1 paper. Solvent systems were butanol–1·5N-aqueous ammonia [13] and ethanol–

[9] Leonard and Owens, *J. Amer. Chem. Soc.*, 1958, **80**, 6039.
[10] Torrey and Brewster, *J. Amer. Chem. Soc.*, 1908, **30**, 862.
[11] (*a*) Woodward, *Angew. Chem.*, 1957, **69**, 50; (*b*) Djerassi and Zderic, *J. Amer. Chem. Soc.*, 1956, **78**, 2907.
[12] Birch and Smith, Chem. Soc. Special Publ. No. 12, 1958, p. 1.
[13] Reid and Lederer, *Biochem. J.*, 1951, **50**, 60.

XUM

aqueous ammonia [14] for mono- and di-carboxylic acids respectively. General instructions for radioactive assay are as for Part XVII.[4]

Curvularin.—*Curvularia* was cultured as previously described [1] except that the glucose concentration was doubled. The crude metabolite was purified by percolation of its ethyl acetate solution through a short column of the earth " Florisil " (Floridin Co., Warren, Pennsylvania) and recrystallisation from chloroform–ether or benzene–methanol. Curvularin was obtained as plates, m. p. 206—207° (Found: *C*-Me, 5·4, 4·6. Calc. for $C_{16}H_{20}O_5$: 1*C*-Me, 5·15%) and had $\nu_{max.}$ (in Nujol) 3290, 1700, 1660, and 1610 cm.$^{-1}$. Curvularin (150 mg.) was heated on the steam-bath under nitrogen in pyridine (5 c.c.) with hydroxylamine hydrochloride (110 mg.) for 2 hr. The gummy product (153 mg.) in ether was filtered through a short " Florisil " column. Crystallisation from benzene–ether gave curvularin oxime as the benzene *solvate*, m. p. 188—190° (Found: C, 68·1; H, 6·95; N, 3·8. $C_{16}H_{21}O_5N,C_6H_6$ requires C, 68·5; H, 7·1; N, 3·6%), $\lambda_{max.}$ 288, $\lambda_{infl.}$ 217 and 248 mμ (log ε 3·40, 4·26, and 3·68 respectively), $\nu_{max.}$ (in Nujol) 3310, 1702, 1630, and 1600 cm.$^{-1}$.

2-5′-*Hydroxyhexyl*-6,8-*dimethoxynaphthalene*-1,3-*diol* (VII).—Di-*O*-methylcurvularin (490 mg.) in 5% methanolic potassium hydroxide (8 c.c.) was heated at 14 mm. for 20 min. on the water-bath. The cooled solution was acidified with 2N-sulphuric acid and left at 0° overnight. The precipitate was repeatedly recrystallised from benzene with " Florisil " as decolorising agent, to give the *naphthol* (VII), m. p. 103—105° (Found: C, 67·9; H, 7·75; OMe, 18·9. $C_{18}H_{24}O_5$ requires C, 67·5; H, 7·55; 2OMe, 19·4%), $\lambda_{max.}$ 244, 291, 294, 302, and 329 (infl.) mμ (log ε 4·89, 3·64, 3·64, 3·65, and 3·40) (Schmid and his co-workers [15] give similar data for related hydroxy- and methoxy-methylnaphthalenes), $\nu_{max.}$ (in Nujol) 3434, 3140, and 1636 cm.$^{-1}$ (in carbon tetrachloride) 3602, 3413, and 1639 cm.$^{-1}$. The naphthol gave a red ferric test, and with acetic anhydride in pyridine for two days gave an alkali-insoluble oil, $\lambda_{max.}$ 237, 288, 322, and 336 mμ (log ε 4·66, 3·82, 3·59, and 3·56), $\lambda_{infl.}$ 262 and 298 mμ (log ε 3·91 and 3·76), $\nu_{max.}$ (in carbon disulphide) 3410, 1763, 1731, 1635, 1250, and 1210 cm.$^{-1}$. The product from the naphthol and an excess of ethereal diazomethane was repeatedly recrystallised from benzene–light petroleum (with " Florisil "), to give the *trimethoxynaphthalene derivative*, m. p. 80—83° (Found: C, 68·4; H, 7·7; OMe, 27·6. $C_{19}H_{26}O_5$ requires C, 68·2; H, 7·8; 3OMe, 27·8%), $\lambda_{max.}$ 246, 290, 314, and 329 mμ (log ε 4·91, 3·75, 3·52, and 3·45), $\lambda_{infl.}$ 297 mμ (log ε 3·68), $\nu_{max.}$ (in carbon disulphide) 3597, 3410, and 1631 cm.$^{-1}$, insoluble in alkali and forming a dark red *picrate* (from benzene), m. p. 134—135° (Found: C, 53·6; H, 5·15; N, 7·5; OMe, 16·4. $C_{25}H_{29}O_{12}N_3$ requires C, 53·3; H, 5·2; N, 7·5; OMe, 16·5%].

Curvularin, treated with 5% aqueous potassium hydroxide as for dimethylcurvularin, gave an amorphous solid, $\nu_{max.}$ (in Nujol) 3360 and 1637 cm.$^{-1}$, which could not be purified owing to very rapid darkening of the solutions in air.

Deoxydihydro-O-*methylcurvularin.*—The product from deoxydihydrocurvularin [2] (730 mg.) and excess of diazomethane in ether–methanol, on recrystallisation from chloroform–ether, gave *deoxydihydromethylcurvularin* (400 mg.), m. p. 193—195° (Found: C, 70·3; H, 8·1; OMe, 10·1. $C_{17}H_{24}O_4$ requires C, 69·9; H, 8·3; OMe, 10·6%), $\nu_{max.}$ (in Nujol) 3353 and 1692 cm.$^{-1}$. The methyl ether was insoluble in alkali and was converted by acetic anhydride in pyridine into an oil, $\nu_{max.}$ (in carbon disulphide) 1765, 1730, and 1214 cm.$^{-1}$, from which the methyl ether was recovered after hydrolysis with 10% ethanolic sulphuric acid.

The methyl ether (90 mg.) in 5% methanolic potassium hydroxide (5 c.c.) was warmed under reduced pressure for 20 min. on the steam-bath. The cooled solution was acidified and kept overnight at 0°. The precipitate (70 mg.) was recrystallised from benzene to give the *acid*, m. p. 109—111° (Found: C, 66·0; H, 8·5; OMe, 9·9. $C_{17}H_{26}O_5$ requires C, 65·8; H, 8·4; 1OMe, 10·0%), $\lambda_{max.}$ 285 mμ (log ε 3·48), $\lambda_{infl.}$ 225 mμ (log ε 3·93), $\nu_{max.}$ (in Nujol) 3360, 3180, and 1689 cm.$^{-1}$, soluble in aqueous sodium hydrogen carbonate, and giving no ferric test.

Fission of Curvularin by Hydriodic Acid.—Curvularin (1 g.) was refluxed for 1·3 hr. with red phosphorus (0·5 g.) in acetic acid (15 c.c.) and hydriodic acid (3 c.c.; *d* 1·6). Water was added and the mixture was extracted with ether. The product was divided into fractions which were soluble in aqueous sodium hydrogen carbonate (A), sodium carbonate (B), and sodium hydroxide (negligible), and insoluble in alkali (C). Fraction A, after being washed with water to remove

[14] Cheftel, Munier, and Macheboeuf, *Bull. Soc. Chim. biol.*, 1952, **34**, 380.
[15] Schmid and Burger, *Helv. Chim. Acta*, 1952, **35**, 931; Ebnöther, Meijer, and Schmid, *ibid.*, 1952, **35**, 911.

acetic acid, was steam-distilled and the product collected with light petroleum. It was obtained as an oil (24 mg.), identified as octanoic acid by the infrared absorption and behaviour on a paper chromatogram. Fraction B (600 mg.), the iodo-acid, was distilled [b. p. 100—110° (bath)/1 mm.], and a portion was converted into the lithium salt, which with *p*-bromophenacyl bromide in hot aqueous ethanol (2 hr.) gave *p*-bromophenacyl iodide, m. p. 97—99°, identical with authentic material prepared by Collet's method.[16]

Raney alloy (800 mg.) was added portionwise with stirring to the iodo-acid (220 mg.) in 5% aqueous sodium hydroxide (25 c.c.). When the reaction had moderated the mixture was heated on the steam-bath for 1 hr. The nickel was removed and the solution poured into 10N-hydrochloric acid. The product was identified as octanoic acid on the basis of the infrared absorption spectrum and paper-chromatographic behaviour. The *p*-bromophenacyl ester, m. p. 65—67°, was identical with authentic material.

Fraction C (14 mg.) had an odour of coconut, and $\nu_{max.}$ (in carbon disulphide) 1780, 1385, and 1181 cm.$^{-1}$ (γ-lactone). Chromic acid oxidised [7] this lactone (4 mg.) to (*a*) a mixture of steam-volatile acids obtained as the ammonium salts and identified by paper chromatography as acetic, propionic and butyric acid (R_F 0·10, 0·20, and 0·29 respectively), and (*b*) an acid, not volatile in steam, identified by paper chromatography as succinic (R_F 0·23). The lactone (10 mg.) was heated under nitrogen with powdered potassium hydroxide (80 mg.) to 380° for 10 min. and kept thereat for a further 15 min. Water was added to the cooled residue, and the acidified solution was steam-distilled. The distillate was neutralised with ammonia and concentrated. Paper chromatography showed the presence of ammonium acetate (trace), propionate and valerate (R_F 0·10, 0·19, and 0·45).

Fission of Curvularin by Hydrobromic Acid.—Curvularin (800 mg.) was refluxed in acetic acid (8 c.c.) and hydrobromic acid (6 c.c.) for 1·3 hr. Water was added, and the solution was saturated with salt and extracted with ether. The product was separated into fractions A, B, and C as in the fission by hydriodic acid. Acidification of the aqueous alkaline solution of fraction A, followed by extraction with light petroleum, gave a bromine-containing oil (300 mg.) which was reductively dehalogenated as for the iodo-acid above, giving octanoic acid identified by the infrared spectrum, paper chromatography, and conversion into the *p*-bromophenacyl ester. The residual aqueous solution was saturated with salt and extracted with ether. Extraction of the resulting red tar (300 mg.) with boiling benzene gave cream crystals, m. p. 124—126°, difficult to purify further, which gave a violet ferric test. These were kept overnight in methanol previously saturated with dry hydrogen chloride. The product was sublimed at 120—130° (bath)/0·05 mm. and recrystallised from benzene, to give methyl 3,5-dihydroxyphenylacetate, m. p. 109—111° undepressed by a synthetic sample [8] (Found: C, 59·6; H, 5·55. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5%). The infrared spectra of the samples were identical.

Fraction B (120 mg.) contained more of the above bromine-containing acid. Fraction C (60 mg.) contained the γ-lactone isolated from the hydriodic acid fission.

Oxidation of Curvularin.—(i) Chromic acid oxidised [7] curvularin (20 mg.) to acetic acid as the only steam-volatile acid, identified by paper chromatography.

(ii) To curvularin (50 mg.) in 0·1N-aqueous sodium hydroxide (6 c.c.) was added 30% hydrogen peroxide (3 c.c.). After 4 hr. excess of oxidant was destroyed with 5% palladium–charcoal (10 mg.) in the presence of a trace of ferric chloride. The catalyst was removed and aqueous sodium hypoiodite was added. After 30 min. at room temperature the solution was acidifed and excess of oxidant was destroyed with sodium hydrogen sulphite. Continuous ether-extraction gave a product containing two (probably monocarboxylic) acids (R_F in ethanol–aqueous ammonia 0·52 and 0·66). Reoxidation with aqueous sodium hypoiodite gave iodoform, m. p. 120° after sublimation at 110°/10 mm., and an acid fraction containing pimelic acid (R_F 0·35). Recrystallisation of this fraction from benzene–light petroleum gave pimelic acid, m. p. 102—104° undepressed by an authentic specimen of m. p. 104—106°.

(iii) Potassium permanganate (300 mg.) was added with stirring to curvularin (50 mg.) in 3% aqueous sodium hydroxide (10 c.c.) at 0°. Further oxidant (200 mg.) was added portionwise with stirring during 1 hr., and the mixture was then warmed at 60° for 3 hr. Sodium hydrogen sulphite was added to the cooled acidified mixture, and aqueous sodium hypoiodite was added to the resulting clear solution. After 40 min. the solution was worked up as under (ii), to give a mixture containing succinic, glutaric, adipic and pimelic (trace) acid (R_F 0·18, 0·22, 0·27, and 0·31 respectively).

[16] Collet, *Bull. Soc. chim. France*, 1900, **23**, 830.

XUM

Oxidation of deoxydihydrocurvularin as under (i) and (ii) above gave, respectively, acetic acid and a mixture of succinic, glutaric, adipic, and pimelic acid.

Degradation of [^{14}C]*Curvularin.*—Relative molar activities (*a*) and (*b*) below refer to the labelled metabolite and its degradation products derived from $CH_3 \cdot {}^{14}CO_2Na$ and $H \cdot {}^{14}CO_2Na$ respectively. Theoretical numbers of labelled carbon atoms in substances of the $CH_3 \cdot {}^{14}CO_2Na$ series are based on the distribution given by head-to-tail linkage of eight acetate residues.

Curvularia was grown as above except that after 8 days aqueous $CH_3 \cdot {}^{14}CO_2Na$ (0·2 mc) was distributed between two flasks (1·5 l. of medium). The crude curvularin (0·54 g.) isolated after a further 11 days' growth was combined with material obtained by carrier-extraction of the residual culture fluid with pure unlabelled curvularin (total 450 mg.) and then diluted with further unlabelled material. Recrystallisation gave pure labelled curvularin (9·02 g., 7·5 μc, 3·8%) [Found: 10^{-3} r.m.a., (*a*) 322].

The mould was grown as above, aqueous $H \cdot {}^{14}CO_2Na$ (50 μc) being substituted for $CH_3 \cdot {}^{14}CO_2Na$. Medium from 2 culture flasks (1·5 l.) gave [^{14}C]curvularin (0·38 g.; 0·08 μc, 0·16%) [Found: 10^{-3} r.m.a., (*b*) 80·9].

Kuhn–Roth oxidation gave acetic acid, collected as lithium acetate [Found: 10^{-3} r.m.a., $BaCO_3$ (Me), (*a*) 0, (*b*) 9·08; $BaCO_3(CO_2H)$, (*a*) 43·4, (*b*) 1·78. 1*C requires (*a*) 40·3] and converted into the *p*-bromophenacyl ester, m. p. 86° [Found: 10^{-3} r.m.a., (*a*) 42·5, (*b*) 10·8 1*C requires (*a*) 40·3].

Hydrobromic acid fission gave methyl 3,5-dihydroxyphenylacetate [Found: 10^{-3} r.m.a., (*a*) 160. 4*C requires (*a*) 161] and octanoic acid converted into the *p*-bromophenacyl ester [Found: 10^{-3} r.m.a., 163. 4*C requires (*a*) 161].

We are indebted to the Commonwealth Scientific and Industrial Research Organisation (Australia) for a Scholarship (to R. W. R.), to the Rockefeller Foundation and Distillers Co. Ltd., for financial assistance, and to Imperial Chemical Industries Limited for the loan of tracer equipment.

THE UNIVERSITY, MANCHESTER, 13.
THE UNIVERSITY, ABERDEEN.

[*Received, April 20th*, 1959.]

---

639. *Degradative Studies of Peptides and Proteins. Part V.* The Formation of 2-Acylimino-3-methylthiazolid-5-ones from N-Acylthiocarbamoylsarcosine Derivatives and their Behaviour towards Nucleophilic Reagents.*

By D. T. ELMORE.

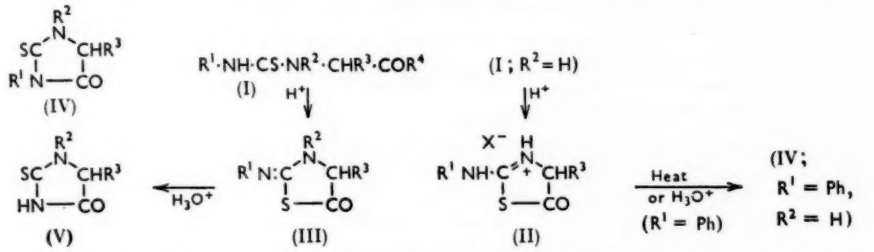
N-Acylthiocarbamoylsarcosine esters and amides undergo cyclisation and degradation in trifluoroacetic acid to 2-acylimino-3-methylthiazolid-5-ones. Scission of the heterocyclic ring is effected by nucleophilic reagents, although less readily than with the salts of 2-acylaminothiazol-5-ones. The former are converted into 2-thiohydantoins by hot, dilute acids.

EDMAN,[1] and Elmore and Toseland,[2] have shown that anhydrous acids cyclise and degrade *N*-phenyl- and *N*-acyl-thiocarbamoylpeptides (I; R^1 = Ph or acyl, R^2 = H) to salts of 2-anilino- and 2-acylamino-thiazol-5-ones (II; R^1 = Ph or acyl) respectively. In the Edman procedure, the *N*-terminal amino-acid is ultimately recovered as a 3-phenyl-2-thiohydantoin (IV; R^1 = Ph, R^2 = H), and it was shown that 2-anilino-4-isobutylthiazolonium hydrochloride (II; R^1 = Ph, R^3 = Bu^i, X = Cl) was converted into 5-isobutyl-3-phenyl-2-thiohydantoin (IV; R^1 = Ph, R^2 = H, R^3 = Bu^i) by either heat or warm, dilute acids. In the latter case, *N*-phenylthiocarbamoyl-leucine (I; R^1 = Ph, R^2 = H, R^3 = Bu^i, R^4 = OH) was an intermediate in the reaction.

* Part IV, *J.*, 1957, 2460.

[1] Edman, *Nature*, 1956, **177**, 667; *Acta Chem. Scand.*, 1956, **10**, 761.
[2] Elmore and Toseland, *J.*, 1957, 2460.

The presence of an additional substituent on the nitrogen atom of peptides containing proline, hydroxyproline, sarcosine, or *N*-phenylglycine as *N*-terminal residues (I; $R^2 \neq H$) precludes the formation of compounds of type (II). There are two possible courses for cyclisation. For *N*-acylthiocarbamoylpeptides, an analogous mechanism involving nucleophilic attack by sulphur on the carbon atom of the peptide linkage would give rise to 2-acyliminothiazolid-5-ones (III; R^1 = acyl). Alternatively, ring-closure could occur on the nitrogen, leading to 3-acyl-2-thiohydantoins (IV; R^1 = acyl). In an earlier



paper,[3] we favoured the second possibility and we concluded that *N*-benzoylthiocarbamoyl-*N*-phenylglycine (I; R^1 = Bz, R^2 = Ph, R^3 = H, R^4 = OH) and its derivatives were cyclised by trifluoroacetic acid to 3-benzoyl-1-phenyl-2-thiohydantoin (IV; R^1 = Bz, R^2 = Ph, R^3 = H), a structure previously advanced by Douglass and Dains.[4] We have now re-examined this problem, using *N*-acylthiocarbamoylsarcosine derivatives (I; R^1 = acyl, R^2 = Me, R^3 = H). Crystallographic analysis by Dr. H. Steeple, of the Department of Physics, Manchester College of Science and Technology, has proved conclusively that the compound obtained by cyclisation of *N*-benzoylthiocarbamoylsarcosine ethyl ester or *p*-toluidide (I; R^1 = Bz, R^2 = Me, R^3 = H, R^4 = OEt or NH·C_6H_4Me-*p*) is 2-benzoylimino-3-methylthiazolid-5-one (III; R^1 = Bz, R^2 = Me, R^3 = H). The molecule is virtually planar, as expected from a consideration of bond angles. Crystallographic data will be published in detail elsewhere. In view of the similarity between the derivatives from sarcosine and *N*-phenylglycine, we now believe that acid-catalysed cyclisation of *N*-benzoylthiocarbamoyl-*N*-phenylglycine and its derivatives affords 2-benzoylimino-3-phenylthiazolid-5-one (III; R^1 = Bz, R^2 = Ph, R^3 = H) and not 3-benzoyl-1-phenyl-2-thiohydantoin (IV; R^1 = Bz, R^2 = Ph, R^3 = H). Our earlier preference for the latter structure depended to some extent on the presence of a strong band at 1527 cm.$^{-1}$ in the infrared spectrum, which we attributed to the $>N-\underset{|}{C}=S$ system.[5] Neither of the 2-aroylimino-3-methylthiazolid-5-ones described herein absorbs over the region where thioureide bands are normally encountered.

N-2,4-Dichlorobenzoylthiocarbamoylsarcosine *p*-toluidide (I; R^1 = 2,4-$Cl_2C_6H_3$·CO, R^2 = Me, R^3 = H, R^4 = NH·C_6H_4Me-*p*) gave the corresponding 2-(2,4-dichlorobenzoylimino)-3-methylthiazolid-5-one (III; R^1 = 2,4-$Cl_2C_6H_3$·CO, R^2 = Me, R^3 = H). Attempts to cyclise *N*-benzoylthiocarbamoylhydroxy-L-proline ethyl ester [I; R^1 = Bz, R^2R^3 = CH_2·CH(OH)·CH_2, R^4 = OEt] in trifluoroacetic acid were unsuccessful, but it is probable that degradation of *N*-phenyl- or *N*-acyl-thiocarbamoyl-prolyl or -hydroxyprolyl peptides in anhydrous acids would involve this type of intermediate.

2-Aroylimino-3-methylthiazolid-5-ones with amines such as *p*-toluidine or cyclohexylamine gave the corresponding *N*-aroylthiocarbamoylsarcosine amide derivatives. In this respect, they are very similar to the 3-phenyl derivative [3] (III; R^1 = Bz, R^2 = Ph, R^3 = H) and the 2-acylaminothiazol-5-ones [2] (II) described previously. 2-Aroylimino-3-methylthiazolid-5-ones, however, unlike the latter, are stable to weaker nucleophiles such

[3] Elmore and Toseland, *J.*, 1956, 188.
[4] Douglas and Dains, *J. Amer. Chem. Soc.*, 1934, **56**, 719.
[5] Elmore, *J.*, 1958, 3489.

XUM

as water and alcohols. Undoubtedly, the replacement of a proton on the heterocyclic ring by an electron-repelling methyl group at $N_{(3)}$ decreases the fractional positive charge on the carbonyl-carbon atom and lowers its susceptibility to nucleophilic attack. Since the *N*-benzoylthiocarbamoyl derivatives of sarcosine ethyl ester and *N*-phenylglycine ethyl ester are cyclised by trifluoroacetic acid, whereas *N*-benzoylthiocarbamoylglycine ethyl ester is unchanged by this treatment, we may summarize the situation by the following expressions:

$$(\text{I};\ R^3 = \text{Me or Ph},\ R^4 = \text{OEt}) + H^+ \underset{k_3}{\overset{k_1}{\rightleftharpoons}} (\text{III}) + \text{EtOH} + H^+ \quad (k_1 \gg k_3)$$

$$(\text{I};\ R^3 = \text{H},\ R^4 = \text{OEt}) + H^+ \underset{k_1}{\overset{k_2}{\rightleftharpoons}} (\text{II}) + \text{EtOH} \quad (k_2 \gg k_1)$$

These inequalities may not always obtain owing to other factors, and this may explain the failure to cyclise *N*-benzoylthiocarbamoyl-L-hydroxyproline ethyl ester. Although the 2-aroylimino-3-methylthiazolid-5-ones are stable to alcohols and water, treatment with hot dilute acids affords 1-methyl-2-thiohydantoin (IV; $R^2 = Me$, $R^3 = H$). This parallels the behaviour of the 3-phenyl derivative (III; $R^1 = Bz$, $R^2 = Ph$, $R^3 = H \longrightarrow$ V; $R^2 = Ph$, $R^3 = H$) described previously.[3]

Attempts to isolate 2-acetylimino-3-methylthiazolid-5-one were unsuccessful. Surprisingly, *N*-acetylthiocarbamoylsarcosine *p*-toluidide (I; $R^1 = Ac$, $R^2 = Me$, $R^3 = H$, $R^4 = NH{\cdot}C_6H_4Me$-*p*) was stable to trifluoroacetic acid. The corresponding benzylamide was apparently cyclised and degraded under these conditions, a result which was expected in view of the stronger basicity of the benzylamide. The subsequent working up procedure, however, involved exposure to water and we surprisingly isolated an acidic product which gave analytical values for *N*-acetylthiocarbamoylsarcosine. The 2-acetylimino-3-methylthiazolidone thus appears to be more sensitive than the corresponding aroylimino-derivatives to nucleophiles. A less likely explanation is the alternative cyclisation to 3-acetyl-1-methyl-2-thiohydantoin and subsequent cleavage with water. Degradation of the benzylamide was also apparently effected by dry hydrogen chloride in nitromethane, but no crystalline material could be isolated. The presence of 2-acetylimino-3-methylthiazolid-5-one (or 3-acetyl-1-methyl-2-thiohydantoin) was confirmed by reaction with *p*-toluidine and the isolation of *N*-acetylthiocarbamoylsarcosine *p*-toluidide.

Experimental

Ultraviolet spectra were determined as before.[6] Infrared spectra were measured in pressed discs of potassium bromide, a rock-salt prism being used.

N-Benzyloxycarbonylsarcosine.—Methylaminoacetonitrile sulphate[7] (30 g.) in 5N-hydrochloric acid (250 c.c.) was heated under reflux for 3 hr. After evaporation under reduced pressure, the residue was dissolved in water (250 c.c.), and sufficient 2N-sodium hydroxide was added to bring the pH to 10—11. The solution was cooled to 0° and stirred while benzyl chloroformate (45 g.) and 2N-sodium hydroxide (135 c.c.) were added alternately portionwise during 45 min. Stirring was continued for 2 hr. without the ice-bath. The solution was extracted with ether, acidified, and extracted three times with chloroform. The extract was dried (Na_2SO_4) and evaporated, and the product (31·6 g.), m. p. 54°, was caused to crystallise by addition of light petroleum (b. p. 40—60°) and storage at 0° (Ben-Ishai and Katchalski[8] report m. p. 53—54°).

N-Benzyloxycarbonylsarcosine p-Toluidide.—A mixture of *N*-benzyloxycarbonylsarcosine (4·46 g.) and triethylamine (2·02 g.) in chloroform (15 c.c.) was cooled to −10°; ethyl chloroformate (2·17 g.) was added portionwise at −10° to −5°. After 30 min., *p*-toluidine (2·14 g.) in chloroform (10 c.c.) was added, and the mixture was allowed to warm to room temperature

[6] Elmore and Ogle, *J.*, 1957, 4404.
[7] Cook and Cox, *J.*, 1949, 2334.
[8] Ben-Ishai and Katchalski, *J. Amer. Chem. Soc.*, 1952, **74**, 3688.

overnight. Enough chloroform was added to obtain a clear solution, which was washed successively with saturated sodium hydrogen carbonate, water, dilute hydrochloric acid, and water, dried (Na_2SO_4), and evaporated. Addition of light petroleum (b. p. 40—60°) afforded the *product* (5·01 g.), which had m. p. 143·5—144·0° after recrystallisation from chloroform–light petroleum (b. p. 40—60°) (Found: C, 69·0; H, 6·6; N, 8·8. $C_{18}H_{20}O_3N_2$ requires C, 69·2; H, 6·5; N, 9·0%).

N-*Benzyloxycarbonylsarcosine Benzylamide*.—This *compound* (80%) was obtained by a similar method from benzylamine. Recrystallised from carbon tetrachloride–light petroleum (b. p. 40—60°), it had m. p. 116·5—117·0° (Found: C, 68·8; H, 6·6; N, 9·4. $C_{18}H_{20}O_3N_2$ requires C, 69·2; H, 6·5; N, 9·0%).

Sarcosine p-*Toluidide Hydrobromide*.—Treatment of *N*-benzyloxycarbonylsarcosine *p*-toluidide (9 g.) in acetic acid (40 c.c.) with 50% w/v hydrogen bromide in acetic acid (20 c.c.) at 100° for a few minutes, followed by cooling, addition of dry ether (400 c.c.), and storage at 0°, furnished this *salt* (7·33 g.), m. p. 262—263° (decomp.) (from ethanol) (Found: C, 46·4; H, 5·7; N, 10·7. $C_{10}H_{15}ON_2Br$ requires C, 46·3; H, 5·8; N, 10·8%).

Sarcosine Benzylamide Hydrobromide.—Prepared in almost theoretical yield by a similar method, this *compound* had m. p. 143·0—143·5° (from ethanol–ether) (Found: C, 46·1; H, 5·9; N, 11·3. $C_{10}H_{15}ON_2Br$ requires C, 46·3; H, 5·8; N, 10·8%).

N-*Acetylthiocarbamoylsarcosine* p-*Toluidide*.—The free base, obtained from treatment of sarcosine *p*-toluidide hydrobromide (2·6 g.) with ammonia in chloroform, was allowed to react with methyl *N*-acetyldithiocarbamate (1·49 g.) in ether (40 c.c.) at room temperature for 3 weeks. The precipitated *product* (2·12 g.) recrystallised from ethanol–light petroleum (b. p. 40—60°), then having m. p. 169° (Found: C, 56·1; H, 6·0; N, 15·7. $C_{13}H_{17}O_2N_3S$ requires C, 55·9; H, 6·1; N, 15·0%).

N-*Acetylthiocarbamoylsarcosine Benzylamide*.—Reaction of sarcosine benzylamide (from the hydrobromide) with methyl *N*-acetyldithiocarbamate in chloroform–ether (1 : 1) during 6 days at room temperature afforded N-*acetylthiocarbamoylsarcosine benzylamide* (49%), which had m. p. 144—145° after recrystallisation first from aqueous ethanol and then from benzene containing a little ethanol (Found: C, 55·7; H, 6·1; N, 15·3. $C_{13}H_{17}O_2N_3S$ requires C, 55·9; H, 6·1; N, 15·0%).

N-*Benzoylthiocarbamoylsarcosine* p-*Toluidide*.—The free base from sarcosine *p*-toluidide hydrobromide (2·6 g.) was treated with benzoyl isothiocyanate (1·63 g.) in ether (20 c.c.). The *product* (3·1 g.) had m. p. 155·5° after recrystallisation from ethanol (Found: C, 63·7; H, 5·6; N, 12·2. $C_{18}H_{19}O_2N_3S$ requires C, 63·3; H, 5·6; N, 12·3%).

N-2,4-*Dichlorobenzoylthiocarbamoylsarcosine* p-*Toluidide*.—Sarcosine *p*-toluidide and methyl *N*-2,4-dichlorobenzoyldithiocarbamate in ether–ethanol (4 : 1) during 5 days at room temperature gave this *compound* (73%), m. p. 172—173°, unchanged by recrystallisation from dioxan (Found: C, 52·9; H, 4·2; N, 10·0. $C_{18}H_{17}O_2N_3SCl_2$ requires C, 52·7; H, 4·2; N, 10·2%).

N-*Benzoylthiocarbamoylhydroxy-*L*-proline Ethyl Ester* (with J. R. Ogle).—A mixture of hydroxy-L-proline ethyl ester hydrochloride (1·22 g.) and triethylamine (0·62 g.) in acetone (10 c.c.) was shaken with benzoyl isothiocyanate (1·10 g.) for 1 hr., then poured into water (80 c.c.). The oily *product* (1·49 g.) solidified and was recrystallised as a monohydrate from ethyl acetate–light petroleum (b. p. 40—60°); it then had m. p. 83—84° (Found: C, 52·6; H, 5·9; N, 8·2; S, 9·4. $C_{15}H_{18}O_4N_2S,H_2O$ requires C, 52·9; H, 5·9; N, 8·2; S, 9·4%). Several attempts to remove the water of crystallisation from this compound gave amorphous materials which did not crystallise. The anhydrous ester was unchanged by treatment with trifluoroacetic acid overnight at room temperature.

2-*Benzoylimino-3-methylthiazolid-5-one*.—(i) A solution of *N*-benzoylthiocarbamoylsarcosine ethyl ester (3 g.) in trifluoroacetic acid (20 c.c.) was set aside overnight. After evaporation under reduced pressure, followed by addition of ether and evaporation, the *product* (2·24 g.) crystallised and had m. p. 158—159° (decomp.) [unchanged by recrystallisation from benzene–light petroleum (b. p. 90—120°)] and $\lambda_{max.}$ 2810 (ε 18,650), $\lambda_{min.}$ 2680 (ε 14,260), $\lambda_{max.}$ 2570 (ε 21,070) in methylene chloride (Found: C, 56·6; H, 4·6; N, 11·5. $C_{11}H_{10}O_2N_2S$ requires C, 56·4; H, 4·3; N, 12·0%).

(ii) A solution of *N*-benzoylthiocarbamoylsarcosine *p*-toluidide (300 mg.) in trifluoroacetic acid (3 c.c.) was left overnight and then poured into water. The product (190 mg.) was collected, washed, and recrystallised, and then had m. p. 157—158°. The two samples had

XUM

identical infrared spectra with bands at 1737, 1621, 1584, 1567, 1436, 1400, 1334, 1312, 1271, 1251, 1165, 1132, 1107, 1069, 1025, 965, 858, and 725 cm.$^{-1}$.

Ring-opening Reactions of 2-Benzoylimino-3-methylthiazolid-5-one.—(i) The thiazolid-5-one (468 mg.) in chloroform (5 c.c.) was allowed to react with cyclohexylamine (198 mg.) in the warm for 5 min. Addition of benzene caused *N-benzoylthiocarbamoylsarcosine cyclohexylamide* (460 mg.) to separate. After two recrystallisations from chloroform–light petroleum (b. p. 40—60°) and one from aqueous ethanol, it had m. p. 166·0—166·5° (Found: C, 61·2; H, 6·5. $C_{17}H_{23}O_3N_3S$ requires C, 61·2; H, 7·0%).

(ii) In a similar manner, reaction of the thiazolid-5-one (468 mg.) with *p*-toluidine (215 mg.) furnished *N*-benzoylthiocarbamoylsarcosine *p*-toluidide (400 mg.). After recrystallisation from ethanol, it had m. p. 155° and the same in admixture with the sample above. The infrared spectra were indistinguishable.

(iii) A solution of the thiazolid-5-one (50 mg.) in ethanol (2 c.c.) and 2N-hydrochloric acid (2 c.c.) was heated under reflux for 2 hr. After evaporation to dryness under reduced pressure, followed by partition between ethyl acetate and saturated sodium hydrogen carbonate, the organic phase was evaporated to give 1-methyl-2-thiohydantoin (12 mg.), m. p. 223·0—224·5° (decomp.), indistinguishable from an authentic sample by paper chromatography in cyclohexane–butan-1-ol–90% acetic acid (3 : 1 : 1).[6]

2-(2,4-Dichlorobenzoylimino)-3-methylthiazolid-5-one.—Degradation of 2,4-dichlorobenzoylthiocarbamoylsarcosine *p*-toluidide in trifluoroacetic acid afforded the *thiazolid-5-one* (92%), m. p. 157—158° [from benzene–light petroleum (b. p. 60—80°)], $\lambda_{max.}$ in CH_2Cl_2, 2840—2880 (ε 18,920), $\nu_{max.}$ 1730, 1634, 1568, 1479, 1435, 1396, 1336, 1289, 1260, 1240, 1151, 1134, 1105, 1046, 961, 883, 865, 848, 789, 779 cm.$^{-1}$ (Found: C, 44·0; H, 3·1; N, 9·4. $C_{11}H_8O_2N_2SCl_2$ requires C, 43·6; H, 2·7; N, 9·2%).

Ring-opening Reactions of 2-(2,4-Dichlorobenzoylimino)-3-methylthiazolid-5-one.—(i) Interaction of the thiazolid-5-one with cyclohexylamine in warm chloroform furnished *N-2,4-dichlorobenzoylthiocarbamoylsarcosine cyclohexylamide* (96%). Recrystallised twice from ethanol–light petroleum (b. p. 40—60°) and once from aqueous ethanol, it had m. p. 174—175° (Found: C, 50·7; H, 5·4; N, 10·3. $C_{17}H_{21}O_2N_3SCl_2$ requires C, 50·8; H, 5·3; N, 10·5%).

(ii) The thiazolid-5-one (100 mg.) was heated in ethanol (2 c.c.) and 2N-hydrochloric acid (2 c.c.) under reflux for 4 hr. Isolation and paper chromatography as described above revealed that a mixture of 1-methyl-2-thiohydantoin and starting material was present.

Attempted Preparations of 2-Acetylimino-3-methylthiazolid-5-one.—(i) *N*-Acetylthiocarbamoylsarcosine *p*-toluidide was recovered from solution in trifluoroacetic acid overnight.

(ii) A solution of *N*-acetylthiocarbamoylsarcosine benzylamide (837 mg.) in trifluoroacetic acid (1 c.c.) was left overnight and then poured into water. An extract thereof by ethyl acetate was washed with water, dried (Na_2SO_4), and evaporated. Addition of light petroleum (b. p. 40—60°) precipitated an oil, which rapidly, but only partly, solidified. The product (335 mg.), recrystallised from ethanol–light petroleum (b. p. 40—60°), had m. p. 149—152° with effervescence. It dissolved in saturated sodium hydrogen carbonate with effervescence and was presumably *N-acetylthiocarbamoylsarcosine* (Found: C, 37·7; H, 5·4; N, 15·0. $C_6H_{10}O_3N_2S$ requires C, 37·9; H, 5·3; N, 14·7%).

(iii) *N*-Acetylthiocarbamoylsarcosine benzylamide (560 mg.) in dry nitromethane (8 c.c.) was treated with dry hydrogen chloride for 10 min. Ether (8 c.c.) was added, and benzylamine hydrochloride (260 mg.), m. p. 244° (decomp.), was removed. The filtrate was evaporated under reduced pressure, and as much hydrogen chloride as possible was removed. *p*-Toluidine (430 mg.) in chloroform (5 c.c.) was added, and the solution was warmed and shaken for 5 min., washed successively with dilute hydrochloric acid, water, saturated sodium hydrogen carbonate, and water, and was then dried. Filtration and evaporation afforded *N*-acetylthiocarbamoyl *p*-toluidide (180 mg.), m. p. and mixed m. p. 169—170°, having the authentic infrared spectrum.

The author is grateful to Imperial Chemical Industries Limited for their financial assistance.

Staveley Research Laboratories,
The University, Sheffield, 10.
Department of Biochemistry,
Queen's University, Belfast

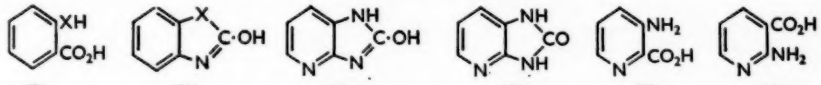
[*Received, April 27th,* 1959.]

640. *Formation of 2′-Hydroxyimidazo(4′,5′:2,3)pyridine from the Hydrazides and Hydroxamic Acids of 2-Aminonicotinic and 3-Aminopicolinic Acids.*

By D. Harrison and A. C. B. Smith.

2′-Hydroxyimidazo(4′,5′:2,3)pyridine (III) is formed in the pyrolysis of either 2-aminonicotinhydroxamic acid or 3-aminopicolinhydroxamic acid. Better yields are obtained from the corresponding hydrazides by the Curtius reaction.

The attempted conversion of *ortho*-substituted carboxylic acids (I; X = –NH– or –O–) into the corresponding amine, *via* the acid amide, hydrazide, or hydroxamic acid, yields 2-hydroxy-benzimidazoles or -benzoxazoles (II).[1] We originally planned to investigate the application of this route to the synthesis of 2′-hydroxyimidazopyridines. However, Dornow and Hahmann[2] recently described the preparation of 2′-hydroxyimidazo-(4′,5′:2,3)pyridine (III) and certain alkyl and aryl derivatives from both hydrazides and amides of the corresponding 2-aminonicotinic acids. In consequence, we have studied only the hydroxamic acids and record here the results obtained on these compounds and on the isomeric hydrazide not studied by Dornow and Hahmann.



(I) (II) (III) (IV). (V) (VI)

The azides from the acids (V) and (VI) decompose smoothly in hot toluene or xylene to give the heterocylic compounds (III). The same product is obtained, but in moderate yield only, by heating 3-aminopicolinhydroxamic acid above its m. p. for a short time. Similar treatment of the isomeric hydroxamic acid gave a difficultly separable mixture of the expected product (III) and 2-aminonicotinic acid.

From the infrared spectrum the amide structure (IV) appears more probable than (III), at least in the solid. Ultraviolet spectra of some of the compounds studied are summarized in the Table.

	In ethanol		In 0·1N-NaOH	
	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$
2-Hydroxybenzimidazole	225·5, 280	7,200, 7,500	242, 285	5,700, 7,800
2′-Hydroxyimidazo(4′,5′:2,3)pyridine	228, 292	3,400, 12,300	234 (inf.), 299·5	2,800, 11,400
Monoacetyl ,, ,,	251, 286	5,800, 10,400		
Diacetyl ,, ,,	238·5, 284	8,800, 9,700 [a]		
2-Aminonicotinic acid			243, 314	9,400, 5,200
Substance A			241, 300	(375), (655) [b]

[a] Approximate values only. Solution in ethanol unstable. [b] $E^{1\%}_{1\,cm.}$

By the action of acetic anhydride on the imidazopyridine (III) either the mono- or the di-acetyl derivative can be obtained. Work on the structure of these compounds and on the acylation of 2-hydroxybenzimidazole will be reported later.

Experimental

2-Aminonicotinic Acid.—Phillips's method[3] was modified by performing the Hofmann reaction on the crude ammonium quinolinamate instead of isolating the free acid.

Preparation and Decomposition of o-Amino-carboxyazides.—3-Aminopicolinhydrazide[5] (1 g.), m. p. 117—119°, in 4N-acetic acid (13 ml.) at 0—5° was treated with aqueous sodium nitrite

[1] (*a*) Stoermer, *Ber.*, 1909, **42**, 3133; (*b*) Scott and Mote, *J. Amer. Chem. Soc.*, 1927, **49**, 2545.
[2] Dornow and Hahmann, *Arch. Pharm.*, 1957, **290**, 20.
[3] Phillips, *Ber.*, 1894, **27**, 839.
[4] Kirpal, *Monatsh.*, 1900, **21**, 957.
[5] Oakes, Pascoe, and Rydon, *J.*, 1956, 1045.

(3·9 ml.) [from sodium nitrite (4·6 g.) and water (40 ml.)]. After 15 min., the product was collected, washed with water, and dried overnight ($CaCl_2$). The crude azide (0·61 g., 56%) had m. p. 116° (explosion). A portion (0·12 g.) in toluene (10 ml.) was heated (oil-bath); first at 90° for a few minutes, then to boiling for 10 min. The brown solid (0·05 g., 50% from azide), after crystallization from ethanol, afforded 2′-hydroxyimidazo(4′,5′ : 2,3)pyridine, m. p. 270—272° not depressed by an authentic sample [6] (lit., m. p. 265—266°; [2,7] 238—239°; [8] 274° [6]) (Found: C, 53·3; H, 3·7; N, 31·3. Calc. for $C_6H_5ON_3$: C, 53·3; H, 3·7; N, 31·1%); $\nu_{max.}$ 1695s (amide I), 1632, 1610, 1492, 1452s, 1047s, 867s, 768s, and 697s cm.$^{-1}$ (potassium bromide disc).

Similarly 2-aminonicotinhydrazide [2,5] was converted into an azide, m. p. 124° (explosion) (lit.,[2] 127°); decomposition in xylene gave the crude 2′-hydroxyimidazopyridine (96% from azide). Also, 2-aminobenzazide [9] was decomposed in toluene to give 2-hydroxybenzimidazole (45%), m. p. 313—316° (lit.,[10] 310—312°) not depressed by an authentic sample from *o*-phenylenediamine and urea; $\nu_{max.}$ 1750s (amide I), 1487s, 1368, 1273, 1200, 1030, 734s, and 704s cm.$^{-1}$ (potassium bromide disc).

Acetylation of 2′-Hydroxyimidazo(4′,5′:2,3)pyridine.—The imidazopyridine (0·15 g.) and acetic anhydride (1 ml.) were refluxed gently for 30 min. After a few minutes' boiling with water (3 ml.) and cooling a *monoacetyl derivative* (0·1 g.) separated. Crystallization from benzene gave needles, m. p. 212—213° (Found: C, 54·3; H, 4·2; N, 23·6. $C_8H_7O_2N_3$ requires C, 54·2; H, 3·9; N, 23·7%). When water was not added a *diacetyl derivative* was obtained, forming needles, m. p. 136—138°, from acetic anhydride (Found: C, 54·7; H, 4·4; N, 19·2. $C_{10}H_9O_3N_3$ requires C, 54·8; H, 4·1; N, 19·2%). The diacetyl compound was hydrolysed to monoacetyl by boiling water, and complete hydrolysis was rapid in hot 0·5N-sodium hydroxide.

2-Aminonicotinhydroxamic Acid.—Cold solutions of hydroxylammonium chloride (13·9 g.) in water (20 ml.) and 20% sodium hydroxide (80 ml.) were mixed. Methyl 2-aminonicotinate [4] (1·2 g.) in methanol (8 ml.) was added to the above solution (9 ml.) and the mixture set aside at room temperature for 7 days. Removal of methanol (reduced pressure) and addition of water (5 ml.) gave a yellow solution, to which acetic acid (1·5 ml.) was added cautiously, precipitating *2-aminonicotinhydroxamic acid* (1·1 g., 91%), m. p. 182—185°. After two recrystallizations from water the acid had m. p. 190°, but complete liquefaction was not observed (Found: C, 46·9; H, 4·8; N, 27·4. $C_6H_7O_2N_3$ requires C, 47·1; H, 4·6; N, 27·4%).

Similarly, ethyl 3-aminopicolinate [5] afforded a *hydroxamic acid* (49%), m. p. 143—145°, (from water) (Found: C, 46·6; H, 4·4; N, 26·9%).

Pyrolysis of o-Amino-hydroxamic Acids.—3-Aminopicolinhydroxamic acid (0·3 g.) was heated for 5 min. at 210—220° (bath-temp.). A solution of the brown residue in water on cooling gave crude 2′-hydroxyimidazopyridine (0·1 g.), m. p. 272—274° after crystallization from ethanol (charcoal). Similarly, 2-aminobenzhydroxamic acid [11] heated at 150—170° for 7 min. gave 2-hydroxybenzimidazole.

2-Aminonicotinhydroxamic acid (3·3 g.), however, when treated similarly gave a crude solid (*A*) (1·8 g.), m. p. 246—248° not raised by repeated crystallization from water, believed to be a mixture of the expected 2′-hydroxy-compound and 2-aminonicotinic acid. Quantitative separation and positive identification of the contaminant has not been achieved. By repeated crystallization from ethanol, least soluble fractions being rejected each time, a small amount of 2′-hydroxyimidazopyridine was obtained. An alternative separation was the isolation of the hydroxy-compound as its monoacetyl derivative. Ultraviolet spectroscopy [12] indicated that (*A*) contained 35—40% of 2-aminonicotinic acid.

The authors thank Mr. P. F. Washbrooke, B.Sc., for determination of infrared spectra.

NOTTINGHAM & DISTRICT TECHNICAL COLLEGE. [*Received, April 27th,* 1959.]

[6] Petrow and Saper, *J.*, 1948, 1389.
[7] Clark-Lewis and Thompson, *J.*, 1957, 442.
[8] Vaughan, Krapcho, and English, *J. Amer. Chem. Soc.*, 1949, **71**, 1885.
[9] Heller and Siller, *J. prakt. Chem.*, 1927, **116**, 9.
[10] Niementowski, *Ber.*, 1910, **43**, 3021.
[11] Scott and Wood, *J. Org. Chem.*, 1942, **7**, 508.
[12] Dewar and Urch, *J.*, 1957, 345.

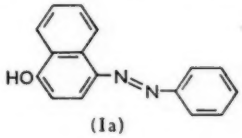
641. *Tautomerism and Geometrical Isomerism of Arylazo-phenols and -naphthols. Part I. 4-Phenylazo-1-naphthol.*

By Ernst Fischer and (Mrs.) Yael F. Frei.

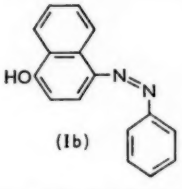
4-Phenylazo-1-naphthol (I) exists in solution as an equilibrium mixture with its tautomer, α-naphthaquinone phenylhydrazone (II). On cooling, this equilibrium shifts towards the latter (in methylcyclohexane) or towards the former (in alcohol). The alcoholic solution at −140° contains practically only the former (I), which on irradiation with light at various wavelengths is photoequilibrated with its *cis*-isomer, in analogy with other azo-compounds. Between −135° and −90° the unstable *cis*-isomer is thermally converted into the stable *trans*-isomer *via* the phenylhydrazone. Each step has an activation energy of about 11 kcal./mole, as compared with about 23 kcal./mole for the normal *cis* ⟶ *trans* conversion. No direct photoconversion involving the hydrazone seems to take place. Similar results were obtained with solutions in tetrahydrofuran–methyltetrahydrofuran.

Kuhn and Baer [1] were the first to point out that 4-phenylazo-1-naphthol (I) exists in solution as a tautomeric equilibrium mixture with the phenylhydrazone (II). Their results were confirmed and extended by several authors.[2]

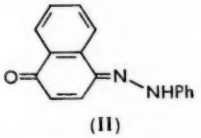
One would expect tautomer (I) to exist in a *cis*- and a *trans*-form (Ia and b) in analogy with azobenzene,[3] the azonaphthalenes,[4] and 4-hydroxyazobenzene,[5,6] but attempts to achieve such isomerisations have hitherto been unsuccessful.[7]



(Ia)



(Ib)



(II)

The present investigation,* by the low-temperature technique,[8,9] was undertaken in order to find evidence for any photoisomerisations and thermal isomerisations (Ia) ⇄ (Ib), and to show if and how such isomerisations are affected by the tautomerism (I) ⇄ (II). The latter point is of particular interest because one can envisage a thermal *cis* ⟶ *trans* isomerisation with the hydrazone as intermediate, *viz.*, (Ib) ⟶ (II) ⟶ (Ia). Such a route may be energetically " cheaper " than the direct route (Ib) ⟶ (Ia).

Spectra in Various Solvents, at Different Temperatures.—Results of such measurements are given in Fig. 1*A*, *B*, *D*. If, with previous authors, we assign the absorption band around 400 mμ to the *trans*-azo-isomer (Ia) and the band around 480 mμ to the hydrazone (II), these results confirm the effect of the solvent on the equilibrium (I) ⇄ (II) reported by Burawoy and Thompson.[10] In addition, they show that cooling has little effect on this equilibrium in toluene or tetrahydrofuran, but shifts it strongly in favour of the hydrazone in methylcyclohexane (Fig. 1*B*), and in favour of the azo-compound in ethanol–methanol

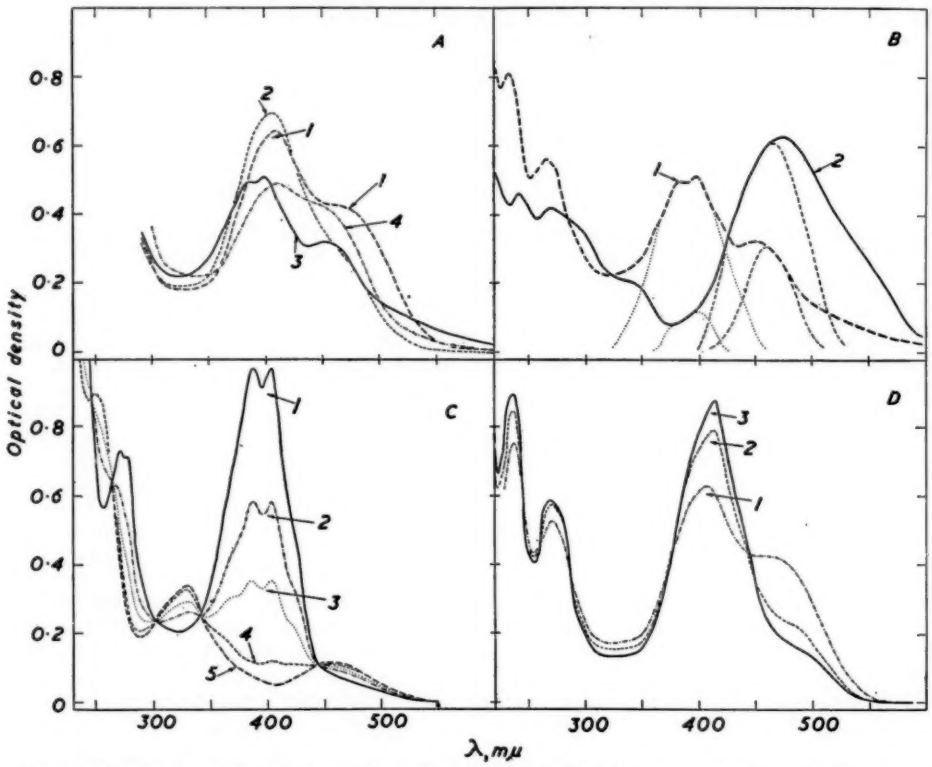
* For a preliminary account see *Bull. Res. Council Israel*, 1958, **7**, *A*, 227.

[1] Kuhn and Baer, *Annalen*, 1935, **516**, 143.
[2] Sawicki, *J. Org. Chem.*, 1957, **22**, 743, where earlier references are listed.
[3] Hartley, *J.*, 1938, 633.
[4] Fischer, Frankel, and Wolovski, *J. Chem. Phys.*, 1955, **23**, 1367.
[5] Schulte-Frohlinde, *Annalen*, 1958, **612**, 138.
[6] Unpublished work.
[7] Brode, Gould, and Wyman, *J. Amer. Chem. Soc.*, 1952, **74**, 4647.
[8] Hirshberg and Fischer, *J.*, 1954, 297.
[9] *Idem*, *Rev. Sci. Instr.*, 1959, **30**, 197.
[10] Burawoy and Thompson, *J.*, 1953, 1443.

XUM

(Fig. 1*D*). The results obtained with the solution in methylcyclohexane, a non-polar solvent, probably indicate a genuine temperature-dependence of the equilibrium (I) $\rightleftharpoons$ (II) and can therefore be used to compute the enthalpy difference between the two tautomers by application of the van't Hoff isochore. Such a computation, the ratio of the absorption bands at 400 and 470 mμ (indicated by thin lines in Fig. 1*B*) being assumed to

FIG. 1. (*A*) *Solutions of* (I) *at room temperature.* 10 *mg./l. in* (1) *ethanol,* (2) *tetrahydro-2-methylfuran, and* (4) *toluene,* (3) *about* 8 *mg./l. in methylcyclohexane (saturated solution).*



(*B*) (1) *As A*(3) *above*; (2) *cooled to* −90°. *Heavy curves depict experimental absorption spectra; thin lines indicate the absorption bands characterising the azo-compound* (*I*) *and the phenylhydrazone* (II), *submerged in the experimental curves.*

(*C*) *Solution* (11·7 *mg./l.*) *of the* O-*methyl ether in methylcyclohexane at* −18°: (1) *before irradiation*; (2), (3), (4) *after photoequilibration at* 436, 365, 405 *mμ*; (5) " cis " *computed from* (4) *and* (1), *on the assumption that the* cis-*isomer has no absorption at* 402 *mμ.*

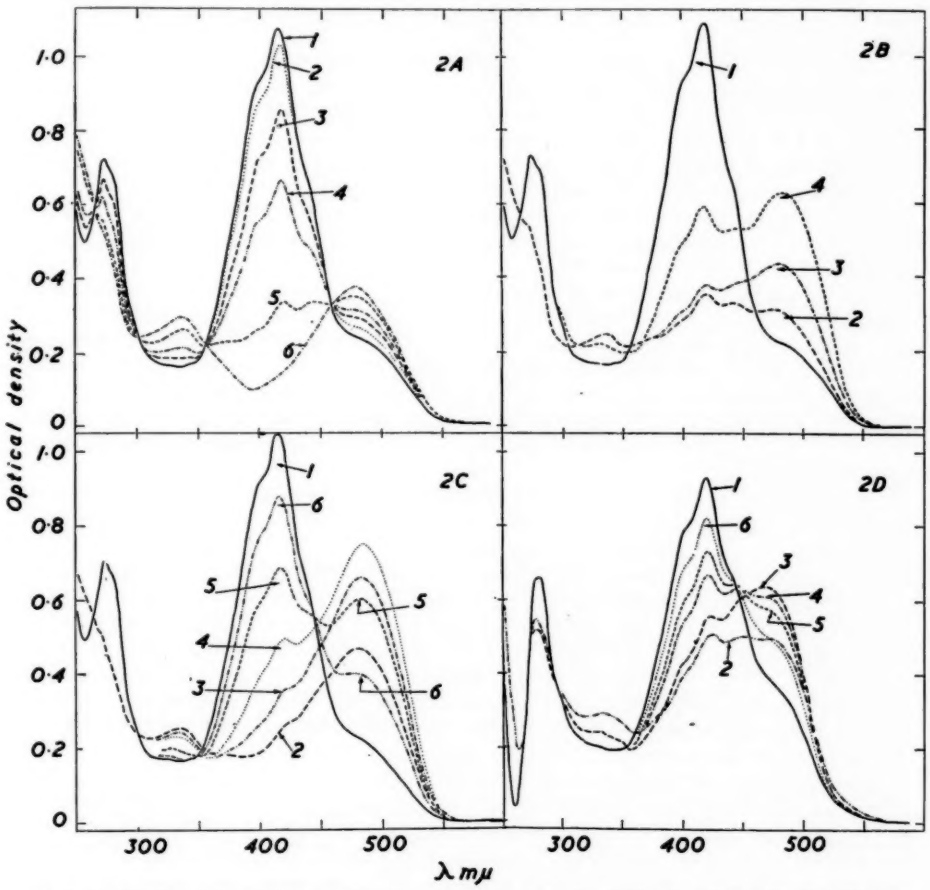
(*D*) *Solution of* (I) (10·2 *mg./l.*) *in ethanol–methanol* (7 : 3) *at various temperatures.* (1) + 20°; (2) −67°; (3) −120°. *The spectrum at* −140° *is practically identical with* (3). *Curves* (2) *and* (3) *are corrected for the thermal contraction at the respective temperatures.*

be proportional to the ratio (I) : (II), gives $2 \pm 0{\cdot}2$ kcal./mole for ΔH in (I) ⟶ (II) + ΔH, and appears to be the first value reported for this reaction.

The temperature-dependence of the spectrum in alcoholic solution (Fig. 1*D*) is probably due to a combination of effects, including the large change in dielectric constant and solute–solvent hydrogen-bonding on cooling. Cooling below −130° causes no further change in the spectrum of the alcoholic solutions, either because tautomerism is no longer possible at lower temperatures, or because it is virtually complete [in favour of (Ia)] at −130°. As

will be shown below, both reasons appear to be correct. In this connection it should be mentioned that the *O*-methyl derivative of the azo-compound (I) has also a submerged absorption band at about 480 mμ (Fig. 1*C*, curve 1).

FIG. 2. (*A*) *Solution of* (I) 10·2 *mg./l.*) *in ethanol–methanol* (7 : 3). (1) *At* −140°; (2), (3), (4), (5) *after photoequilibration at* 546, 365, 436, 405 mμ, *respectively*; (6) " cis " *isomer, computed by assuming arbitrarily that curve* (5) *represents* 80% *of* cis-*compound.*



(*B*) (1) *As in A*(1); (2) *after photoequilibration at* 405 mμ; (3) *after heating to* −118°; (4) *after* 110 *min. at* −118°.

(*C*) (1) *As in A*(1), *at* −120°; (2) *after* 30 *min. irradiation at* 405 mμ; (3), (4) *after* 95 *and* 260 *min., respectively*; (5) *solution heated to* −110° *and kept at this temperature for* 45 *min.*; (6) *same, after another* 50 *min.*

(*D*) *Solution of* (I) (10·3 *mg./l.*) *in tetrahydrofuran–tetrahydro-2-methylfuran* (1 : 1). (1) *At* −135°, *also at* −155°; (2) *after irradiation for* 10 *min. at* 405 mμ, −155°; (3) *after* 30 *minutes' irradiation with* 405 + 436 mμ *at* −135°; (4), (5), (6) *solution* (3) *after* 5, 10, *and* 20 *min., respectively.*

At room temperature ethanolic solutions were found to obey Beer's law at concentrations varying from 6×10^{-4} to $1{\cdot}5 \times 10^{-5}$ moles/l.

Irradiations.—Owing to the low solubility of the azo-compound (I) in methylcyclohexane, the solution of Fig. 1*B* is supersaturated, and irradiation results in crystallisation.

Irradiation of alcoholic solutions at temperatures down to −80° has no effect. At −140°, however, irradiation causes a typical *cis* ⇄ *trans* photoequilibration,[4] with a different photoequilibrium established at each wavelength (Fig. 2*A*). No thermal changes occur at this temperature. The results are closely similar to those obtained with the *O*-methyl ether of the azo-compound (I) at −18°, shown in Fig. 1*C*, and with other azo-compounds.[11] The existence of four well-defined isosbestic points corroborates the above assumption that at −140° the conversion of the hydrazone into the azo-compound is virtually complete, and the curves of Fig. 2*A* describe mixtures, in various proportions, of the *cis*- and *trans*-forms (Ia and b).

When the solution giving Fig. 2*A*, curve 5, is allowed carefully to warm to −120° (Fig. 2*B*) and kept at this temperature, the "*trans*"-band at 416 mμ at first remains almost constant, whereas the "hydrazone" band at 482 mμ is enhanced progressively (curves 3, 4 in Fig. 2*B*). Later, the 416 mμ band gradually increases in intensity too. Warming to −80° results in rapid regeneration of the original spectrum. These results indicate that the *cis*-isomer formed by irradiation at −140°, when warmed to −120°, is converted into the phenylhydrazone (II), the latter then being transformed into the *trans*-isomer. The non-existence of isosbestic points in Fig. 2*B* indicates the presence of a triple mixture of (Ia), (Ib), and (II).

Fig. 2*C* shows the results of irradiation at −120°. Curve 2, taken after cessation of irradiation, indicates that some phenylhydrazone (II) has already been formed during irradiation, as is to be expected from Fig. 2*B*. Formation of the hydrazone continues (curves 3, 4), but is soon counter-balanced by the concurrent conversion of this compound into the *trans*-azo-form (Ia) (curve 5). Curve 6 shows how the original spectrum is eventually approached. The existence of isosbestic points at 445 and 350 mμ during the later stages (curves 4, 5, 6) indicates that by then only two compounds exist in solution, namely (II) and (Ia).

Irradiation at −110° results in a mixture already rich in the hydrazone. At this temperature, conversion of the *cis*-isomer into the hydrazone is already much faster than the conversion of the latter into the *trans*-isomer.

Cooling, to −140°, of any of the mixtures depicted by the curves in Figs. 2*B* and 2*C* stops any further spontaneous reaction, indicating that both thermal steps, (Ib) ⟶ (II), and (II) ⟶ (Ia), do not take place any more at this temperature. If the solution giving Fig. 2*C*, curve 5 [constituting a mixture of (II) and (Ia)], is cooled to −140° and irradiated with light at 546 mμ, the spectrum is not affected. This proves that photoisomerisation (II) ⟶ (I) also does not take place at this temperature. Together with the results of Fig. 2*A* this makes it probable that the only photoconversion taking place at −140°, as well as at higher temperatures, is (Ia) ⇄ (Ib).

In order to find out whether or not the above phenomena are peculiar to solutions in a hydroxylic solvent, similar experiments were carried out in a mixture of tetrahydrofuran and its 2-methyl derivative. Fig. 2*D* shows that, qualitatively, the results in this solvent resemble those obtained with alcoholic solutions. However, in order to stop all thermal reactions, it is necessary to go down to at least −155°. At this temperature the solvent mixture tends to crystallise, whereas at −150° thermal isomerisations already set in. It was therefore experimentally impossible to do more than establish the basic similarity between the phenomena in hydroxylic and non-hydroxylic polar solvents.

The spectral data for the azo-compound and its *O*-methyl ether are summarised in the Table.

Kinetic Experiments.—The kinetics of the *cis* ⟶ *trans* thermal conversion of the *O*-methyl ether was investigated in methylcyclohexane in the temperature range 27·5° ($\tau_{\frac{1}{2}} = 25$ min.) to 70° ($\tau_{\frac{1}{2}} = 0{\cdot}25$ min.). The conversion was found to be a first-order reaction, with Arrhenius constants $A = 10^{13{\cdot}3}$ sec.$^{-1}$, $E = 22{\cdot}9$ kcal./mole in $k = Ae^{-E/RT}$. These values closely resemble those reported for other arylazo-compounds. *E.g.*, Halpern

[11] Fischer and Frei, *J. Chem. Phys.*, 1957, **27**, 328.

Spectral data for 4-phenylazo-1-naphthol (I) in ethanol–methanol, and its O-methyl ether in methylcyclohexane.

	Maxima		Isosbestic points	
	λ (mμ)	$10^{-3}\varepsilon$	λ (mμ)	$10^{-3}\varepsilon$
trans-(I) at −140°	470 *	4·8	*cis-trans*	
	416	21·0	457	6·5
	272	14·5	355	4·4
cis-(I) at −140°			301	4·8
	477	7·5	265	11·7
	336	5·9		
(II), calc. from Fig. 2*C* †	483	*ca.* 22	hydrazone-*trans* (I)	
	335	*ca.* 5	445	11·3
	245 *	—	*ca.* 350	*ca.* 3·9
O-Me ether of (I) at −18°	402 } 386 }	20·7	*cis-trans*	
			443	2·3
trans	276 } 268 }	15·0	340	5·4
			302	5·0
	236	25·0	263	13·7
cis	453	2·4	244	19·0
	329	7·0	232	23·6

* Inflexion. † Curve 5 in Fig. 2*C* is assumed to correspond to a mixture of (II) (40%) and *trans*-(I) (60%).

et al.[12] found for azobenzene in a large variety of solvents E between 22·8 and 24·7 kcal./mole and log A between 12·9 and 13·7.

For the azo-compound (I) in alcoholic solution it proved possible, by careful manipulation of the temperature, to differentiate to a considerable extent between the two consecutive steps (Ib) ⟶ (II) and (II) ⟶ (Ia), and to measure their kinetics separately. Both steps were found to be of the first order with regard to the compound being transformed, with estimated Arrhenius constants $A = \sim 10^{13\cdot5}$ sec.$^{-1}$, $E = 12$ kcal./mole for the first step, and $A = 10^{11}$ sec.$^{-1}$, $E = 11$ kcal./mole for the second. The following values of half-life times give an idea of the measurements involved. Step one: at −124°, 493 min.; at −110°, 15 min. Step two: at −110°, 55 min.; at −85°, 0·9 min.

With solutions of the azo-compound (I) in tetrahydrofuran–methyltetrahydrofuran, no quantitative kinetic measurements could be made, beyond those indicated in Fig. 2*D*.

Conclusions.—The above results strongly indicate that with 4-phenylazo-1-naphthol the *cis* ⟶ *trans* conversion proceeds *via* the phenylhydrazone, and that this two-step low-energy mechanism is preferred to the one-step high-energy mechanism operative in other azo-compounds. A similar mechanism may be operative in other hydroxyazo-compounds and aminoazo-compounds.

Experimental

Irradiations and spectrophotometric determinations were carried out in special Dewar-type cells, in a Cary Model 14 Recording Spectrophotometer.[9] The irradiation source was a 125 w Mazda type MB/U mercury lamp (with its envelope removed) housed in an elliptic reflector. The mercury lines were isolated by combinations of Corning filters (578, 546, 436, 365 mμ) or interference filters (405, 300 + 313 mμ). The concentrations given in the Figures are at room temperature, uncorrected for contraction on cooling, unless stated otherwise. Photoequilibrations required 10—100 min., depending on the wavelength of the photoactive light.

4-Phenylazo-1-naphthol was prepared according to Witt and Dedichen's directions,[13] its *O*-methyl ether according to those of Zincke and Bindewald.[14]

The authors are indebted to Professor Y. Hirshberg for discussions, to Mr. M. Kaganovitch for synthesising the above two compounds, and to Mrs. Nelly Castel for technical assistance.

Laboratory of Photochemistry and Spectroscopy, The Weizmann Institute of Science, Rehovot, Israel. [*Received, March 18th*, 1959.]

[12] Halpern, Brady, and Winkler, *Canad. J. Res.*, 1950, **28**, 140.
[13] Witt and Dedichen, *Ber.*, 1897, **30**, 2655.
[14] Zincke and Bindewald, *Ber.*, 1884, **17**, 3026.

XUM

642. *Peroxides of Elements other than Carbon. Part V.*[1] *The Formation of Cadmium Peroxides by Autoxidation and by Nucleophilic Substitution.*

By Alwyn G. Davies and J. E. Packer.

Alkylperoxycadmium compounds can be prepared by the reaction of cadmium alkyls with molecular oxygen, or with alkyl hydroperoxides.

Similar reaction with hydrogen peroxide gives products containing the Cd·O·O·Cd group.

The only peroxides of cadmium so far reported are compounds of indefinite composition, usually prepared by treating cadmium hydroxide with aqueous hydrogen peroxide.[2] We have now investigated the autoxidation of cadmium alkyls, and their nucleophilic substitution by alkyl hydroperoxides and by anhydrous hydrogen peroxide, as routes to the peroxides of cadmium.

Autoxidation of Cadmium Alkyls.—Dimethylcadmium in air absorbed oxygen, giving a glass which exploded when touched. In cyclohexane, approximately 1 mol. of oxygen was absorbed slowly at room temperature, giving a product containing 1 mol. of peroxide. The reaction appeared to be catalysed by a trace of pyridine, and was slower in ether but faster in anisole.

Diethylcadmium and dibutylcadmium are much more reactive. In ether, approximately 2 mol. of oxygen were absorbed, essentially all forming peroxide. A white solid separated after 1 mol. of oxygen had been taken up. In cyclohexane, rather less oxygen was absorbed, giving a deficiency of peroxide in the case of diethylcadmium.

It would therefore appear that these cadmium alkyls undergo autoxidation in a manner (and perhaps by a mechanism) similar to that of the Grignard reagents [3] and boron alkyls,[4,1] *i.e.*:

$$R_2Cd \xrightarrow{O_2} \underset{(I)}{RCd{\cdot}O{\cdot}OR} \xrightarrow{O_2} \underset{(II)}{Cd(O{\cdot}OR)_2} \quad . \quad . \quad . \quad . \quad (1)$$

Dimethylcadmium gives the peroxide (I; R = Me), whereas diethyl- and dibutylcadmium are more reactive and form the insoluble peroxides (II; R = Et or Bu). To confirm this structure, the precipitate obtained by autoxidation of diethylcadmium was treated with terephthaloyl chloride; diethyl diperoxyterephthalate [5] was isolated, confirming the presence of the ethylperoxy-group. Similarly, in the hydrolysate of the autoxidation product of dibutylcadmium (II; R = Bu), butyl hydroperoxide was identified by gas–liquid chromatography.[6,4]

When diethylcadmium was allowed to absorb 1 mol. of oxygen, the product (I; R = Et) was stable. This suggests that when the amount of peroxide formed is less than the amount of oxygen taken up, the reduction occurs intermolecularly between dialkylcadmium and an alkylperoxycadmium group.

Reaction of Cadmium Alkyls with Hydroperoxides.—Whereas boron alkyls do not react with protic reagents, cadmium alkyls undergo nucleophilic substitution, liberating the alkane. A possible route to the cadmium peroxides might therefore be of the type:

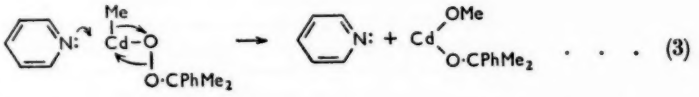
$$R'O{\cdot}OH + RCd{\cdot} \longrightarrow R'O{\cdot}OCd{\cdot} + RH \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Reduction of the peroxide by the alkyl cadmium might complicate this simple picture.

[1] Part IV, Davies and Hare, *J.*, 1959, 438.
[2] Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green & Co., London, 1923, Vol. IV, p. 532.
[3] Walling and Buckler, *J. Amer. Chem. Soc.*, 1955, **77**, 6032.
[4] Part III, Abraham and Davies, *J.*, 1959, 429.
[5] Baeyer and Villiger, *Ber.*, 1901, **34**, 738.
[6] Abraham, Davies, Llewellyn, and Thain, *Analyt. Chim. Acta*, 1957, **17**, 499.

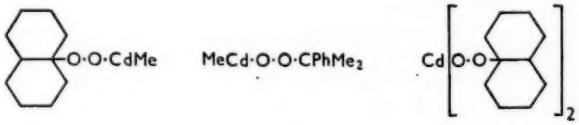
Treatment of dimethylcadmium in cyclohexane * with 1 mol. of decahydro-9-naphthyl hydroperoxide caused evolution of 1 mol. of methane and separation of 9-decalylperoxymethylcadmium (III), which did not melt without decomposition. It could not be redissolved in any aprotic solvent, and with acetic acid rapidly liberated 1 mol. of methane.

(αα-Dimethylbenzylperoxy)-methylcadmium (IV) was prepared similarly from αα-dimethylbenzyl hydroperoxide, and showed similar properties. When it was kept at 50° overnight with a trace of pyridine, the peroxide content fell by three quarters with an equivalent loss of CdMe groups (as measured by the evolution of methane by acetic acid). This can reasonably be interpreted as involving nucleophilic migration of an alkyl group from the metal to oxygen (eqn. 3) as we have postulated for similar boron [4,1] and silicon peroxides.[7]



. . . (3)

The reaction of diethyl- and dibutyl-cadmium with hydroperoxides was more vigorous. Both alkyl groups tended to be displaced, though some active alkyl groups were lost in reduction of the peroxide. For example, 2 mol. of 9-decalyl hydroperoxide with diethyl-



(III) (IV) (V)

cadmium gave 1·8 mol. of ethane, and 0·2 mol. of peroxide was reduced. As we observed in the autoxidation reactions, precipitation of the dialkylperoxycadmium compounds started as soon as the second alkylperoxy-group was introduced. From the reaction of 9-decalyl hydroperoxide with diethylcadmium and with dibutylcadmium, partially reduced bisdecalylperoxycadmium (V) was obtained as an amorphous white powder; it was insoluble in all unreactive solvents. On hydrolysis, 9-decalyl hydroperoxide was isolated.

Similar reaction between cadmium dialkyls and anhydrous hydrogen peroxide in inert solvents might provide a route to cadmium peroxides, such as RCd·O·O·CdR and CdO_2. By this type of reaction, Perkins [8] obtained from diethylcadmium a compound which he supposed to have the composition $3CdO,H_2O_2$, and which exploded under reduced pressure.

Dimethylcadmium (2 mol.) and hydrogen peroxide (1 mol.) in ether liberated approximately 2 mol. of methane; the product gave a further 2 mol. of methane with acetic acid. The compound MeCd·O·O·CdMe is thus apparently being formed, but no attempt was made to isolate it.

The reaction between equimolecular amounts of hydrogen peroxide and diethyl- or dimethyl-cadmium in ether was complete in a few seconds, and in different experiments, between 1·2 and 1·6 mol. of alkane were collected. A white solid separated, with a peroxidic oxygen : cadmium ratio of up to 0·84 : 1. It appears then that these products contain a substantial amount of cadmium peroxide, CdO_2, but that the substitution reaction is accompanied by some reductive rearrangement of the alkyl group. An attempt was made to minimise this by conducting the reaction at −20°. The product from one such reaction decomposed violently under vacuum, giving brown cadmium oxide; from a second reaction a compound with a peroxidic oxygen : cadmium ratio of 0·78 : 1 was isolated.

* It was found that nitromethane reacts with dimethylcadmium according to the equation: $2CH_3{\cdot}NO_2 + Me_2Cd \longrightarrow 2MeH + Cd(CH_2{\cdot}NO_2)_2$. The dry product is explosive.

[7] Part I, Buncel and Davies, *J.*, 1958, 1550.

[8] Perkins, *J.*, 1929, 1687.

XUM

An attempt was made to cause reaction between hydroperoxides and cadmium salts in an inert solvent; the above type of reduction could not then occur. Anhydrous sodium αα-dimethylbenzyl peroxide in toluene could be obtained by adding the hydroperoxide to sodium methoxide in toluene and removing methanol under reduced pressure. Attempts to prepare alkylperoxycadmium compounds by treating this peroxide with a cadmium salt, particularly the iodide or acetate, were unsuccessful.

Experimental

The usual explosion precautions were observed in reactions involving peroxides.[7] Cadmium peroxides were handled in an anhydrous atmosphere in a glove box.

Analysis.—Peroxidic oxygen. Organoperoxides were determined iodometrically in propan-2-ol,[7] and hydrogen peroxide and other non-organic peroxides similarly but in aqueous solution.

Cadmium. The sample was added to an excess of a standard solution of disodium dihydrogen ethylenediaminetetra-acetate, and the excess determined by titration of the solution, buffered to pH 10, with a standard Zn^{++} solution, Eriochrome Black T being used as indicator.[9]

Alkylcadmium groups. MeCd and EtCd groups were estimated by hydrolysis with acetic acid; the paraffin was evolved quantitatively, and its volume measured in the gas burette (see Fig. 2, Part III [4]). When appropriate, the capsules were broken into the solvent containing acetic acid by the technique described previously, or the acetic acid was added *via* the tap *C*;[4] anisole (saturated with the appropriate paraffin) was a convenient solvent because it can readily be dried and has a low vapour pressure.

Preparation of Materials.—The cadmium dialkyls were prepared by treating the appropriate Grignard reagent with anhydrous cadmium chloride, and the products isolated by distillation and stored under nitrogen in glass capsules (see Part III [4]) at low temperature. All the compounds fumed violently, but did not ignite, when exposed to air.

Dimethylcadmium (72% yield), b. p. 63°/205 mm., is difficult to separate from the last traces of ether. Analysis for cadmium showed it to be 94·4% pure. It was stored at −20°, no decomposition occurring during 6 months. With an excess of butanol in cyclohexane, 1·09 mol. of methane were evolved in 3 hr., and a compound presumably MeCd·OBu formed in solution; acetic acid liberated a further 0·96 mol. of methane.

Autoxidation of cadmium alkyls.

Solvent	Time (hr.)	O_2 absorbed (mol.)	Peroxide formed (mol.)	Solvent	Time (hr.)	O_2 absorbed (mol.)	Peroxide formed (mol.)
	Dimethylcadmium				*Diethylcadmium*		
Et_2O	16	0·00	—	Et_2O	1	1·90	1·97
Et_2O	5	*a*	0·58	cyclo-C_6H_{12}	0·75	1·74	1·52
cyclo-C_6H_{12}	20	1·12	1·02				
cyclo-C_6H_{12} [b]	2	1·18	1·13		*Dibutylcadmium* [d]		
PhOMe	1	1·0 [c]	—	Et_2O	1	2·00	1·93
				cyclo-C_6H_{12}	1	1·63 [c]	1·58

[a] Oxygen was dispersed through a sintered-glass plate into the solution. [b] In the presence of one drop of pyridine. [c] More oxygen was absorbed slowly at 60°. [d] Assumed to be 83% pure. This reaction may be incomplete because a bulky gelatinous precipitate prevented stirring.

Diethylcadmium, mixed with ether, was distilled at 1 mm. into a trap cooled in liquid nitrogen from the reaction mixture in a bath slowly heated to 120°. The ether was removed into a second cold trap. At room temperature the diethylcadmium (55% yield) slowly deposited grey cadmium. It was stored at −80°, and no further decomposition occurred. Quantitative hydrolysis showed it to be 96·5% pure; it catalysed the polymerisation of methyl methacrylate both in the presence and in the absence of oxygen.

Dibutylcadmium (12% yield), extracted similarly, also decomposed at room temperature but not at −80°. It was not analysed because the evolution of butane could not be accurately measured and because an analysis for cadmium would have yielded no useful information. A lower limit to the purity of 83% can be derived from the maximum values of the oxygen absorbed and the peroxide formed, during autoxidation.

Pentane, cyclohexane, and ether were dried over sodium wire and distilled immediately

[9] Schwarzenbach, "Complexometric Titrations," (trans. Irving) Methuen, London, 1957, p. 83.

before use. Anisole and toluene were heated under reflux with molten sodium for 3 hr., then distilled as required.

Reaction of Cadmium Alkyls with Oxygen.—Thin glass capsules containing 0·2—0·8 g. of the appropriate cadmium alkyl were broken in solvent (*ca.* 50 c.c.) under oxygen in the apparatus described in Fig. 2, Part III.[4] Typical experiments are listed in the Table; others are described individually below. In all solvents used, a precipitate appeared as soon as more than 1 mol. of oxygen was absorbed.

Dimethylcadmium with no solvent. A capsule of the cadmium alkyl was broken in air in the gas burette. A glassy solid was deposited on the walls of the flask; when it was touched with the stirrer, it exploded, breaking the apparatus.

Diethylcadmium: identification of the ethylperoxy-group. Diethylcadmium (0·7736 g.) was autoxidised in ether, and the solid was allowed to settle. The ether was decanted, and the solid shaken with terephthaloyl chloride (0·5 g.) in benzene (20 c.c.) until the yellow colour of the acid chloride disappeared. The cadmium chloride and the excess of diethylperoxycadmium were filtered off, and the benzene was removed from the filtrate under reduced pressure, leaving an oil which was crystallised twice from light petroleum giving diethyl diperoxyterephthalate, m. p. 31·5—32·5° (Found: C, 57·6; H, 5·9. Calc. for $C_{12}H_{14}O_6$: C, 56·7; H, 5·55%). Baeyer and Villiger [5] give m. p. 37°; our sample probably contained some monoperoxy- or nonperoxy-ester as impurity.

Diethylcadmium: oxygen in limited supply. By using two burettes to circulate air through the flask, diethylcadmium (0·5421 g.) was allowed to absorb 0·91 mol. of oxygen; the supply of gas was then discontinued; 0·69 mol. of peroxide had been formed, and persisted for 42 hr. at room temperature, even in the presence of a trace of pyridine. If it is assumed that the difference between the amount of oxygen absorbed and that of the peroxide formed is due to the reaction $EtCd\cdot + EtO\cdot OCd\cdot \longrightarrow 2EtO\cdot Cd\cdot$, it follows that diethylcadmium must be the reducing agent, and that the molecular balance of the various groups present is EtCd, 0·87; EtO·OCd, 0·69; EtO·Cd, 0·44.

Dibutylcadmium: identification of the butylperoxy-group. Oxygen was passed through an ethereal solution of dibutylcadmium (0·65 g.) for 1 hr., a white solid being precipitated. The product was hydrolysed with 4N-hydrochloric acid (25 c.c.) for 2 hr., and the ethereal layer washed and dried. The ether was removed and the residual liquid analysed by gas–liquid chromatography.[5,4] n-Butyl hydroperoxide was identified by comparison with an authentic specimen.

Reaction of Cadmium Alkyls with Hydroperoxides.—Capsules of the cadmium alkyl were broken in a solvent containing the hydroperoxide and saturated with the appropriate alkane. The volume of alkane evolved was measured, and the amount of peroxide estimated iodometrically. The amount of RCd group remaining could be determined by measuring the further evolution of alkane with acetic acid.

Dimethylcadmium and 9-decalyl hydroperoxide. In cyclohexane, 1 mol. of dimethylcadmium with an excess of the hydroperoxide gave 1 mol. of methane. A second mol. was evolved when acetic acid was added. When the reaction was conducted in pentane, crystals separated during 3 hr. Next day they were washed with pentane and dried *in vacuo*, giving 9-decalylperoxymethylcadmium; it became brown at *ca.* 93°, and sintered at *ca.* 150°, but did not melt (Found: C, 43·3; H, 7·0; Cd, 36·8; peroxidic O, 9·9. Calc. for $C_{11}H_{20}O_2Cd$: C, 44·5; H, 6·8; Cd, 37·9; peroxidic O, 10·8%). It could not be dissolved in any aprotic solvent, and no further purification was possible.

Dimethylcadmium and αα-dimethylbenzyl hydroperoxide. Dimethylcadmium with 2 mol. of the hydroperoxide in cyclohexane similarly gave 1·25 mol. of methane, without loss, even after 24 hr., of peroxide; acetic acid yielded a further 0·75 mol. of methane. With 1 mol. of the hydroperoxide in cyclohexane, 1·07, 1·09, and 1·08 mol. of methane were evolved in different experiments. The solvent was removed under reduced pressure, giving methyl-(αα-dimethylbenzylperoxy)cadmium as white crystals which were washed with cyclohexane and dried; they became brown at *ca.* 150°, but did not melt below 240°. Again no solvent could be found for recrystallisation (Found: C, 40·0; H, 4·9; Cd, 36·8; peroxidic O, 11·3. Calc. for $C_{10}H_{14}O_2Cd$; C, 43·1; H, 5·0; Cd, 40·3; peroxidic O, 11·5%). At 50° in the presence of a trace of pyridine the peroxide content fell by three-quarters overnight, with an equivalent loss of MeCd groups.

Diethylcadmium and αα-dimethylbenzyl hydroperoxide. With 2 mol. of the hydroperoxide, 1·51 mol. of ethane were evolved and 0·53 mol. of peroxide was reduced.

Diethylcadmium and 9-decalyl hydroperoxide. With 2 mol. of the hydroperoxide in cyclohexane, 1·83 mol. of ethane were evolved, and partially reduced di-9-decalylperoxycadmium was obtained as a white powder (Found: Cd, 25·6; peroxidic O, 11·1. Calc. for $C_{20}H_{34}O_4Cd$; Cd, 25·0; peroxidic O, 14·2%). Hydrolysis with 2N-sulphuric acid liberated 9-decalyl hydroperoxide, m. p. and mixed m. p. 84—86°.

Diethylcadmium and t-butyl hydroperoxide. With 2 mol. of the hydroperoxide in anisole, 1·54 mol. of ethane were evolved slowly, and a further 0·30 mol. on the addition of acetic acid.

Dibutylcadmium and αα-dimethylbenzyl hydroperoxide Because of the high solubility of butane in organic solvents (up to 1 l. of gas per 50 c.c. of solvent) and its sensitivity to temperature variations, measurement of the volume of butane evolved during reaction was not possible.

Dibutylcadmium in pentane containing αα-dimethylbenzyl hydroperoxide under nitrogen gave a precipitate within 5 min. After 3 hr. the solvent was removed under reduced pressure, and the residue hydrolysed with aqueous acetic acid. No butane was evolved, showing that no BuCd groups remained.

Dibutylcadmium and 9-decalyl hydroperoxide. From the reaction between dibutylcadmium and the hydroperoxide (2 mol.), partially reduced bis-9-decalylperoxycadmium was obtained (Found: Cd, 26·5; peroxidic O, 11·7%).

Aliquot portions of a similar mixture were analysed periodically for peroxide, the mixture being stirred vigorously during sampling after solid had separated (30 min.). The results were as follows:

Time (min.)	0	10	21	32	87	Next day
Peroxide (mol.)	2·00	1·85	1·78	1·71	1·66	1·44

Reaction of Cadmium Alkyls with Hydrogen Peroxide.—The powdered dry urea–hydrogen peroxide complex was kept at 60°/1 mm., and 98% hydrogen peroxide was collected in a trap at −40°.

Dimethylcadmium. With dimethylcadmium (1 mol.), hydrogen peroxide in ether gave 1·60 mol. of methane within 5 sec., and a white precipitate separated (Found: Cd, 74·2; peroxidic O, 16·5. Calc. for CdO_2: Cd, 77·8; peroxidic O, 22·2%).

In an attempt to minimise the amount of reduction, the experiment was repeated at low temperature. Reaction occurred when the cold mixture was allowed to warm to −20°. The precipitate was separated, but decomposed violently under reduced pressure in the desiccator, giving clouds of a fine brown powder, presumably cadmium oxide. When dried in a stream of air, the solid could be analysed (Found: peroxidic O, 15·9%).

Diethylcadmium. The reaction between diethylcadmium and hydrogen peroxide (1 mol.) in ether was again very fast, and 1·2 mol. of ethane were evolved. The white precipitate was washed and dried (Found: Cd, 59·8; peroxidic O, 14·2%).

Preparation of Anhydrous Sodium αα-Dimethylbenzyl Peroxide in Toluene.—The sodium salt, prepared by treating the hydroperoxide with aqueous sodium hydroxide, is hydrated. The following method of preparing the salt in toluene may be useful when the anhydrous reagent is required.

Sodium was dissolved in toluene by adding the minimum possible amount of methanol. The hydroperoxide (1 mol. with respect to sodium) was then added, and the methanol removed by concentrating the solution to half volume under reduced pressure. A peroxide determination shows that about 5% of the peroxide is decomposed in this process.

Attempts to prepare alkylperoxycadmium compounds by treating this solution with anhydrous cadmium salt, particularly the iodide or acetate, were not successful.

The Reaction between Dimethylcadmium and Nitromethane.—A capsule of dimethylcadmium was broken in nitromethane. After about 10 min., methane (2 mol.) was evolved and a yellow solid separated. The dry solid detonated whilst being handled in the glove box; with careful manipulation it could be analysed [Found: Cd, 45·2. Calc. for $Cd(CH_2{\cdot}NO_2)_2$: Cd, 48·3%]. The same compound was apparently formed when an attempt was made to recrystallise (αα-dimethylbenzylperoxy)methylcadmium from nitromethane.

We are indebted to Professors E. D. Hughes, F.R.S., and Sir Christopher Ingold, F.R.S., for interest and encouragement. This work was carried out during the tenure (by J. E. P.) of a Commission in the New Zealand Defence Scientific Corps.

William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1. [*Received, March 18th*, 1959.]

643. *Mechanism of Hydrogenation. Part II.*[1] *Acid Catalysis of Hydrogenolysis of Epoxides and of Allyl Alcohol Derivatives.*

By F. J. McQuillin and W. O. Ord.

Hydrogenolysis of a series of epoxides at platinum is acid catalysed. Hydrogenolysis *via* the conjugate acid is a rational explanation of this evidence and the steric results. Hydrogenolysis and anionotropic rearrangement of allyl alcohols and their derivatives have parallel features, suggesting a similar reaction intermediate. Hydrogenolysis of α-eudesmol is shown to be acid catalysed.

Catalytic hydrogenolysis of steroid oxides has two interesting features: the principal product is, as a rule, the derived axial alcohol (cf. Table 1) and the solvent has an important influence. Thus (i) in acetic acid 4,5-epoxycoprostan-3α-ol yields cholestan-3α,4β-diol but in alcohol yields coprostan-3α,5β-diol and with difficulty,[2] (ii) 2,3α-epoxycholestane is reduced in acetic acid but not in alcohol or dioxan,[3] (iii) 1,2α-epoxy-3-oxocholestane,[4] and 4,5β-epoxy-3-oxocoprostane [2] are reduced at both centres in acetic acid, but selectively at the keto-group in neutral solvent. Observation (i) corresponds with the orientating effect of acid as against neutral or alkaline reagents in heterolysis of an oxide,[5] and with (ii) and (iii) suggests that acetic acid may facilitate hydrogenolysis by acid catalysis.

Table 1.

Oxide	Product *	Ref.	Oxide	Product *	Ref.
		Cholestane Series			
1,2α-Epoxy-3-oxo	1,3α- and 1α,3β-diols	*a*	4,5β-Epoxy-3-oxo	3,4β-diol	*d*
			4,5β-Epoxy-3α-hydroxy	3α,4β-diol	*d*
2,3α-Epoxy	3α-ol	*b*	3β-Acetoxy-5,6α-epoxy	3β-acetoxy-5α-ol	*e*
2,3β-Epoxy	2β-ol	*b*	3β-Acetoxy-5,6β-epoxy	3β-acetoxy-6β-ol	*e*
3,4α-Epoxy	3α-ol	*c*	5,6α-Epoxy-3α-hydroxy	3,5α-diol	*f*
		Methyl Cholanate Series			
3α-Acetoxy-11,12α-epoxy	3α-acetoxy-12α-ol	*g*	3α-Acetoxy-11,12β-epoxy	3α-acetoxy-11β-ol	*g*

* At platinum in acetic acid.

[a] Striebel and Tamm, *Helv. Chim. Acta*, 1954, **37**, 1094. [b] Plattner and Furst, *ibid.*, 1949, **32**, 275. [c] Furst and Scotoni, *ibid.*, 1953, **36**, 1332. [d] Plattner, Heusser, and Kulkarni, *ibid.*, 1948, **31**, 1822. [e] Plattner, Petrzilka, and Lang, *ibid.*, 1944, **27**, 513. [f] Plattner, Furst, Koller, and Kuhn, *ibid.*, 1954, **37**, 258. [g] Berner and Reichstein, *ibid.*, 1946, **29**, 1374.

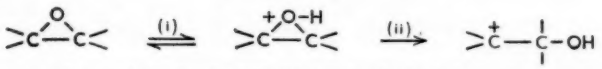
The following observations are relevant. Cyclohexene oxide, 1-methylcyclohexene oxide, 1,2-dimethylcyclohexene oxide, styrene oxide and 5,6-epoxycholestan-3β-ol at platinum in acetic acid are reduced at a satisfactory rate. With the same catalyst in ethyl acetate hydrogen uptake is slow but addition of a trace of strong acid initiates rapid absorption. In dioxan cyclohexene oxide is not reduced and addition of acid is ineffective. As acid catalyst we used a trace of sulphuric acid with the steroid oxide, and with the remainder, 60% perchloric acid. The epoxycholesterol gave cholestane-3β,5α-diol as in acetic acid,[6] styrene oxide gave phenethyl alcohol, 1-methylcyclohexene oxide gave *cis*- and *trans*-2-methylcyclohexanols in closely equal amounts, and in acetic acid the same products. Kotz and Hoffmann [7] reported the hydrogenation of 1-methylcyclohexene oxide in acetic acid to *trans*-2-methylcyclohexanol, which they regard as the sole product. Infrared spectroscopy of our mixed product and its 3,5-dinitrobenzoate did not indicate any third component, *e.g.*, 1-methylcyclohexanol or 1-methylcyclopentylmethanol.

[1] Part I, preceding paper.
[2] Plattner, Heusser, and Kulkarni, *Helv. Chim. Acta*, 1948, **31**, 1822.
[3] Plattner and Furst, *ibid.*, 1949, **32**, 275.
[4] Striebel and Tamm, *ibid.*, 1954, **37**, 1094.
[5] Cf. Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 341.
[6] Plattner, Petrzilka, and Lang, *Helv. Chim. Acta*, 1944, **27**, 513.
[7] Kotz and Hoffmann, *J. prakt. Chem.*, 1935, **110**, 101.

XUM

It seems reasonable to attribute the parallel effect of acidified ethyl acetate and acetic acid to acid catalysis of hydrogenolysis. Dioxan as a relatively basic solvent is known to act as a proton buffer, *e.g.*, in aromatic nitration.[8]

Acid-induced oxide ⟶ ketone rearrangement followed by reduction does not provide a general interpretation: a cholestan-5α-ol could not arise in this way; an oxo-group concomitantly reduced does not yield exclusively the axial alcohol (cf. Table 1); such rearrangement can be induced by strong acid,[9] but only exceptionally by acetic acid.[10] The sequence:



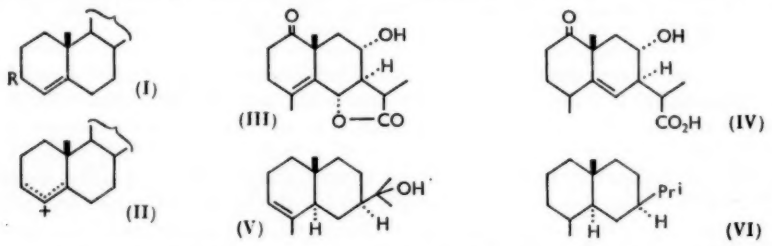
[step (ii) being rate determining] which initiates hydrolysis [11] and rearrangement in acid solution, provides a cationic intermediate, intrinsically more reducible than the oxide, and *a priori* permitting hydrogen transfer to either face of the molecule. The mixed product from 1-methylcyclohexene oxide, and stereospecific reduction of the steroid oxides, dependent on axial lysis [12] and hydrogen transfer to the less hindered face, are consistent with this model.[13]

Acid catalysis of hydrogenolysis of allyl and benzyl alcohols is well known. The yield of hydrocarbon from hydrogenation of cholest-4-en-3α-ol and cholest-4-en-3β-ol and derivatives [14] (I) (cf. Table 2) in ethyl acetate (i) alone or (ii) with addition of perchloric acid increases in the series R = OH < OAc < Cl, *i.e.*, with increasing dipole, and for the more basic groups, R = OH > OAc, in acid solution. The parallel with anionotropic mobility [15] is marked:

TABLE 2. *Yields on hydrogenation of cholest-4-ene derivatives* (I).

I, R =	(i)	(ii)	I, R =	(i)	(ii)
3α-OH	17	94	3β-OH	3	96
3α-OAc	36	85	3β-OAc	37	91
			3βCl	100	—

Where the hydrogenolysed group is a stable anion, acid catalysis and alkali inhibition should be minimised. Reduction [16] of ψ-santonin (III) proceeds at the same rate, and to give the same product (IV), in acid or alkaline solution. This example and the reduction



of 7-methoxycholest-5-en-3β-ol to cholesterol, *i.e.*, without allylic rearrangement,[17] are useful in showing that hydrogenolysis is not merely a concomitant of reduction of the

[8] Benford and Ingold, *J.*, 1938, 929.
[9] Cf. Wendler, Graber, Snoddy, and Bollinger, *J. Amer. Chem. Soc.*, 1957, **79**, 4476; Alexander and Dittmer, *ibid.*, 1951, **73**, 1665.
[10] Cf. Barton, Brooks, and Holness, *J.*, 1951, 278.
[11] Cf. Long and Pritchard, *J. Amer. Chem. Soc.*, 1956, **78**, 2663, 2667; Long, Pritchard, and Stafford, *ibid.*, 1957, **79**, 2362.
[12] Cf. Barton and Cookson, *Quart. Rev.*, 1956, **10**, 67.
[13] Cf. McQuillin, *Chem. and Ind.*, 1957, 251.
[14] Agashe, Shoppee, and Summers, *J.*, 1957, 3107.
[15] Cf. ref. 5, p. 586.
[16] Cf. Clemo and Cocker, *J.*, 1946, 30; Dauben and Hance, *J. Amer. Chem. Soc.*, 1955, **77**, 2451.
[17] Henbest and Jones, *J.*, 1948, 1798.

double band, nor is migration of this bond essential. The evidence appears to be consistent with a process such as (I; R = $\overset{+}{O}H_2$, $H\overset{+}{O}Ac$, OAc, or Cl) ⟶ (II) as initiating hydrogenolysis. Shielding by the departing group will account for the proportion of coprostane obtained in the 3α-substituted series.[14]

Semmler and Risse [18] describe the hydrogenation of α-eudesmol (V) to eudesman (VI) with platinum in acetic acid. We found, after rapid reduction of the double bond, slow hydrogenolysis strongly catalysed by addition of a little perchloric acid.

The behaviour of epoxides and of allyl alcohol (and a tertiary alcohol) towards acid conditions is suggestive of reduction *via* a cationic species.

Experimental

Hydrogenations.—These were carried out in a differential apparatus as in Part I, Adams's platinum oxide catalyst being used.

(I) *In ethyl acetate* (3 *c.c.*). The initial hydrogen uptake (c.c./min.) is recorded (i) in the solvent alone, and (ii) after addition of 60% perchloric acid (1 drop).

Oxide of	Weight (mg.)	Catalyst (mg.)	Uptake (i)	Uptake (ii)	Temp.
Cyclohexene	35	8	0·06	0·3	17°
1-Methylcyclohexene	40	8	0·05	0·6	17
1,2-Dimethylcyclohexene	40	8	0·1	0·4	17
Styrene	42	8	0·05	0·3	18
Cholest-5-en-3β-ol	60	10	0·02	0·2 *	22

* Catalyst—sulphuric acid (2 drops/100 c.c. of ethyl acetate).

(II) *In acetic acid* (30 *c.c.*).

Oxide of	Weight (mg.)	Catalyst (mg.)	Uptake	Temp.
Cyclohexene	349	73	2·1	21°
1-Methylcyclohexene	392	82	3·1	20
1,2-Dimethylcyclohexene	392	73	3·0	17

(III) *In dioxan* (30 *c.c.*). In this solvent with platinum oxide (0·074 g.) cyclohexene oxide (0·348 g.) took up hydrogen (~0·15 c.c./min.); this rate was not increased by addition of perchloric acid.

Reduction Products.—From 1-methylcyclohexene oxide. (*a*) The product of reduction in ethyl acetate containing perchloric acid had b. p. 73—80°/22 mm., n_D^{20} 1·4599, and gave in good yield a 3,5-dinitrobenzoate, m. p. 83—85° (Found: C, 54·7; H, 5·3. Calc. for $C_{14}H_{16}O_6N_2$: C, 54·6; H, 5·2%). Jackman, MacBeth, and Mills [19] give for *cis*- and *trans*-2-methylcyclohexanol, respectively, n_D^{20} 1·4649 and n_D^{20} 1·4616, and for the 3,5-dinitrobenzoates, respectively, m. p. 117° and m. p. 101°. Fractionation of our mixed 3,5-dinitrobenzoate gave *trans*-2-methylcyclohexyl 3,5-dinitrobenzoate, m. p. and mixed m. p. 117°. *trans*-2-Methylcyclohexanol from the sodium–alcohol reduction of the ketone [20] was inverted [21] *via* the toluene-*p*-sulphonate to give the *cis*-alcohol (3,5-dinitrobenzoate, m. p. 100°). From the mixed melting point diagram of the 3,5-dinitrobenzoates our material, m. p. 83—87°, which showed all the infrared bands characteristic of both isomers, was estimated to contain ~58% of the *trans* ester.

(*b*) The product of reduction [7] of 1-methyl*cyclo*hexene oxide, palladised charcoal in acetic acid being used, gave a 3,5-dinitrobenzoate, m. p. 77—80°, *i.e.*, containing closely equal amounts of *cis*- and *trans*-2-methylcyclohexyl 3,5-dinitrobenzoates.

Styrene oxide. This, when reduced in ethyl acetate containing perchloric acid gave phenethyl alcohol, characterised as the 3,5-dinitrobenzoate, m. p. 106° (lit.,[22] m. p. 106°).

5,6α-*Epoxycholestan*-3β-*ol.* This (0·201 g.) when reduced in ethyl acetate–sulphuric acid gave a product which yielded, on chromatography, cholestane-3β,5α-diol,[6] m. p. 224°, $[\alpha]_D$ +

[18] Semmler and Risse, *Ber.*, 1913, **46**, 2303.
[19] Jackman, MacBeth, and Mills, *J.*, 1949, 1717.
[20] Wallach, *Annalen*, 1903, **329**, 373.
[21] Gough, Hunter, and Kenvon, *J.*, 1926, 2052; Huckel and Hagenguth, *Ber.*, 1931, **64**, 2892.
[22] Ruggli, Steiger, and Schobel, *Helv. Chim. Acta*, 1945, **28**, 333.

XUM

16·2° (*c* 0·18) (40 mg.), cholestane-3β,5α,6β-triol,[23] m. p. 236°, $[\alpha]_D$ −2·1° (*c* 0·19) (70 mg.) (3,6-di-acetate, m. p. 167°), and more easily eluted material (50 mg.).

ψ-Santonin. This (0·261 g.) was reduced at about the same rate by palladised charcoal (0·05 g.) in alcohol (30 c.c.) (*a*) alone, or (*b*) with 60% perchloric acid (2 drops), or (*c*) with potassium hydroxide (0·1%), giving in each case dihydro-ψ-santonin,[16] m. p. 188°, $[\alpha]_D$ −5·7° (in acetic acid, *c* 3·98).

α-*Eudesmol*,[24] which was reduced at platinum in acetic acid to the dihydro-derivative, was further reduced after addition of 60% perchloric acid (1%), giving eudesman,[18] b. p. 62—64°/0·2 mm., n_D^{18} 1·4838, $[\alpha]_D$ +12·9° (Found: C, 86·7; H, 13·3. Calc. for $C_{15}H_{28}$: C, 86·6; H, 13·4%).

We thank the Department of Scientific and Industrial Research for an award (to W. O. O.) and Dr. J. D. Parrack for the reduction of α-eudesmol.

KING'S COLLEGE, NEWCASTLE UPON TYNE. [*Received, November 4th*, 1958.]

[23] Westphalen, *Ber.*, 1915, **48**, 1064: Plattner and Lang, *Helv. Chim. Acta*, 1944, **27**, 1872.
[24] McQuillin and Parrack, *J.*, 1956, 2973.

---

644. *The Effect of Viscosity on the Fluorescence Yield of Solutions.*

By E. J. BOWEN and S. F. A. MISKIN.

The fluorescence yields of several solutes in ethylene glycol, water–glycerol and water–sucrose solutions have been measured, and found to increase with increasing viscosity of the liquid. The effect, however, is very dependent both on the solute and on the nature of the solvent.

IT has been found recently that the quantum yields of fluorescence of dilute solutions are raised if the viscosity of the solvent is increased.[1,2] This effect is to be distinguished from the influence of high viscosity in diminishing collisions in a solution between fluorescent molecules and active quenching agents, such as unexcited molecules or dissolved oxygen.[3] The functional relation between yield F and solvent (macro) viscosity η is still imperfectly known. For diphenylmethane dyes in aqueous glycerol–dextrose solutions the process of electronic energy degradation is proportional to $1/\eta$ while for *meso*-substituted anthracene derivatives in paraffins it is proportional to $1/\eta^{0.25}$. Expressing it empirically as $1/\eta^n$ we have $F = \eta^n/(\eta^n + \text{constant})$. A number of other fluorescent solutes in water–glycerol or –sucrose solutions and in ethylene glycol have been examined for viscosity effects.

The concentrations (about 10^{-4}M) of fluorescent solute were adjusted to give equal values (0·1) of the product of extinction coefficient and concentration for the exciting light of wavelength 3660 Å, so that each solution absorbed the same (small) fraction of the incident light beam. Fluorescence emerging at 90° to the exciting beam from a small rectangular cell of the solution was collected by the slit of a constant-deviation spectrometer, fitted with a photomultiplier, so that the fluorescence spectrum could be obtained. By calibration, a lamp of known colour temperature being used, the spectra were plotted as wave-number against relative numbers of quanta emitted per equal interval of wave-number, so that areas were true measures of relative fluorescence yield. Corrections for refractive-index differences were made [4] by multiplying by (refractive index).[2]

Errors due to re-absorption of fluorescence were insignificant at the concentrations used. Absolute yields were obtained by comparison with a solution of sodium 4-amino-naphthalene-1-sulphonate in 97% glycerol, for which F is close to unity. The above

[1] Oster and Nishijima, *J. Amer. Chem. Soc.*, 1956, **78**, 1581.
[2] Bowen and Sahu, *J. Phys. Chem.*, 1959, **63**, 4.
[3] "Fluoreszenz Organischer Verbindungen," Förster, Göttingen, 1951, p. 192.
[4] Hermans and Levinson, *Amer. J. Opt. Soc.*, 1951, **41**, 460.

empirical law was found to hold approximately for viscosities that are not too high; at very high viscosities polarization due to non-rotation of the excited molecules reduces the intensity observable at 90° to the incident light beam. Table 1 gives values for F and n.

TABLE 1. *Sodium salts in water–glycerol (G) and water–sucrose (S) solutions.*

	F (water)	n (G)	n (S)
4-Aminonaphthalene-1-sulphonate	0·71	0·95	0·11
5-Aminonaphthalene-1-sulphonate	0·11	0·24	
8-Aminonaphthalene-2-sulphonate	0·27	0·16	
8-Aminonaphthalene-1-sulphonate	0·03	0·24	
2-Aminonaphthalene-1-sulphonate	0·10	0·21	
5-Aminonaphthalene-2-sulphonate	0·56	0·17	
7-Aminonaphthalene-1,3-disulphonate	0·73	0·15	
5-Dimethylaminonaphthalene-1-sulphonate	0·38	0·41	0·18
8-Dimethylaminonaphthalene-2-sulphonate	0·22	0·53	
Anthracene-2,6-disulphonate	0·51	0·13	
Anthracene-2,7-disulphonate	0·20	0·07	

From these results it appears that the viscosity dependence, as measured by the n value, varies greatly for different solutes, in a way unrelated to the magnitude of F, and that it also varies with solvent. To examine the latter point, measurements were made of fluorescence yields in four solvents of equal viscosity (20 cp. at 20°), ethylene glycol, glycerol–water (70·2% of the former by weight), a sucrose–water solution (52·4% of the former by weight), and a solution of the cellulosic polymer " Cellofas B " in water. Table 2 gives the results.

TABLE 2. *Values of F for solutions of viscosity* 20 *cp. at* 20°.

Solute	Ethylene glycol	Glycerol–water	Sucrose–water	Cellofas B–water	(Water (viscosity = 1 cp)
Sodium 4-aminonaphthalene-1-sulphonate	0·98	0·94	0·79	0·71	0·71
Sodium 5-aminonaphthalene-1-sulphonate	0·51	0·24	0·15	0·11	0·11
Sodium 5-dimethylaminonaphthalene-1-sulphonate	0·70	0·63	0·51	0·38	0·38
2-1′-Naphthyl-5-phenyloxazole	0·78	0·55	0·19	insol.	insol.

For each solute, the first three columns are not equal, although the solvents had equal macro-viscosities. There is a steady fall in F values across the Table. The results can be interpreted on the following lines. The four solvents from left to right have increasing differences between their macro- and micro-viscosities due to increasing " structural " effects. A " Cellofas B " solution is an extreme example; it contains relatively large aqueous regions of low viscosity associated with polymer chains which enhance the macro-viscosity, while ethylene glycol is more homogeneous on a molecular scale. For a non-radiational change-over of an excited molecule to the triplet or ground level, some particular configuration must be achieved, and one part of the molecule may then be regarded as undergoing a diffusion process with respect to another. In a medium of nonhomogeneous micro-viscosity, these movements may be free to occur in the regions of lower viscosity, and the apparent dependence of deactivation on a power less than unity of the reciprocal macro-viscosity may be an empirical expression of this. It is noteworthy that in some instances the value of n approaches unity (Table 1 and ref. 1), indicating that the effect is fundamentally of diffusional character. The variation of n with solute in any one solvent, however, cannot yet be related intelligibly to differences in molecular structure.

PHYSICAL CHEMISTRY LABORATORY,
SOUTH PARKS ROAD, OXFORD.

[*Received, June 1st,* 1959.]

XUM

645. *Liquid-phase Photolysis. Part I. Variation of Isomer Ratios with Radical Source in the Phenylation of Isopropylbenzene. Photolytic Generation of Phenyl Radicals.*

By J. McDonald Blair, D. Bryce-Smith, and B. W. Pengilly.

Photolysis of iodobenzene in isopropylbenzene gives a mixture of isomeric isopropyldiphenyls in the same ratio as is obtained when dibenzoyl peroxide decomposes in isopropylbenzene. Diphenylmercury and tetraphenyl-lead give a different ratio of these isomers when photolytically decomposed in isopropylbenzene. Variations in the product ratio are briefly discussed. An apparatus useful for the study of solution photolysis is described.

Several groups of workers [1,2,3] found the main products of decomposition of dibenzoyl peroxide in isopropylbenzene to be benzoic acid, benzene, 2,3-dimethyl-2,3-diphenylbutane (" dicumyl "), a mixture of the isomeric isopropyldiphenyls, and a high-boiling residue. They differ, however, in their estimates of product ratios. From the published descriptions of the methods of estimating these, it appears that the results of Hey, Pengilly, and Williams [1] are the most accurate, and their figures are used here for comparison.

It has been found that iodobenzene, diphenylmercury, and tetraphenyl-lead can be photolytically decomposed in isopropylbenzene to give products which show that free

Table 1.

Radical source		Ph_2Hg		Ph_4Pb	PhI		$(BzO)_2$
Expt. no.		1	2	3	4	5	
Temp.		120°	120°	120°	120°	120°	80°
Wt. (g.) of radical source		5·035	4·998	3·698	6·001	6·001	10
Isopropylbenzene (ml.)		41	43	44	43	43	150
Irradiation time (hr.)		6	6	12·5	6	6	—
Decomp. (%)		94	63	43·5	82	97	100
Ph radicals produced (g.)		2·06	1·37	0·96	1·86	2·20	4·08
Benzene produced (g.)		1·06	0·79	0·71	0·95	1·27	2·0
Diphenyl fraction (g.)		1·19	0·83	0·60	0·93	1·31	4·66
Composition (%) of diphenyls:	2-	7·7	8·5	5·7	18·1	26·6	
dicumyl fraction	3-	19·4	17·9	13·2	25·7	36·4	
	4-	9·6	9·5	6·9	15·6	19·7	
	d	63·3	64·2	74·1	40·7	17·3	60·5
Residue (g.)		1·30	0·87	0·38	0·41	0·40	2·29
Ph radicals giving benzene (%)		50·8	56·8	73·1	50·4	57·0	48·4
Ph radicals giving diphenyls (%)		8·33	8·55	6·38	11·65	19·35	17·7
Residue : Ph radicals (w/w)		0·630	0·635	0·390	0·225	0·180	0·560
Benzene accounted for as dicumyl (%)		46·5	44·5	41·0	26·0	11·5	92·5
Yield (%) of dicumyl		23·5	26·0	30·1	13·0	6·5	44·5
Ratios (%) of isopropyldiphenyls:	2-	21·0	23·5	22·0	31·0	32·0	31
	3-	53·0	50·0	51·0	43·0	44·0	42
	4-	26·0	26·5	27·0	26·0	24·0	27

Table 2. *Mol. of principal products per mol. of phenyl radicals.*

Expt. no.	1	2	3	4	5
Benzene	0·51	0·57	0·73	0·50	0·57
Isopropyldiphenyls (*a*)	0·085	0·085	0·065	0·115	0·195
" Dicumyl " (*b*)	0·12	0·13	0·15	0·065	0·035
Mol. of benzene not accounted for by (*a*) and (*b*)	0·185	0·225	0·365	0·255	0·305

phenyl radicals are involved in the reactions. The solvent undergoes both side-chain and nuclear attack, with the production of benzene, 2,3-dimethyl-2,3-diphenylbutane, a mixture of the isomeric isopropyldiphenyls, and a high-boiling residue, together with free

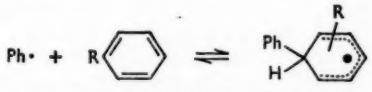
[1] Hey, Pengilly, and Williams, *J.*, 1956, 1463.
[2] Dannley and Zaremsky, *J. Amer. Chem. Soc.*, 1955, **77**, 1588.
[3] Rondestvedt and Blanchard, *ibid.*, p. 1769.

iodine (fixed as silver iodide), and mercury and lead respectively. In the Tables, experimental details and results are summarized and compared with the results of Hey, Pengilly, and Williams [1] for the decomposition of dibenzoyl peroxide in isopropylbenzene.

The ratios of 2- and 3-isopropyldiphenyl obtained from diphenylmercury and tetraphenyl-lead on one hand, and from iodobenzene and dibenzoyl peroxide on the other, seem to fall into two distinct groups. The differences are 7·5—11% for the 2-isomers and 6—11% for the 3-isomers. The experimental error in the analytical procedure is difficult to assess accurately without many more data; but the internal consistency is *ca.* ±2%, which is a normal range for estimations of this type. The authors accordingly feel it probable that the observed discrepancy, although small, is real. The Tables show that the other product ratios are also subject to variation. About 50% of the phenyl radicals from iodobenzene, diphenylmercury, and dibenzoyl peroxide gave benzene. More than 70% of those from tetraphenyl-lead gave benzene, and this, coupled with an increased yield of 2,3-dimethyl-2,3-diphenylbutane (" dicumyl " in the Table), indicates that phenyl radicals from tetraphenyl-lead preferentially attack the side chain of isopropylbenzene, although the ratio of nuclear isomers was almost identical with that observed when diphenylmercury was the radical source. As judged from the relative rates of decomposition of diphenylmercury and tetraphenyl-lead (see Table 1), the stationary concentration of free phenyl radicals must have been much the lower with tetraphenyl-lead as radical source. Foster and Williams [4] have observed rather similar variations of product ratios with concentration of decomposing dibenzoyl peroxide in isopropylbenzene. The low and variable yield of 2,3-dimethyl-2,3-diphenylbutane from the photolysis of iodobenzene in isopropylbenzene probably has as its cause a reaction between αα-dimethylbenzyl radicals and iodine to give 1-iodo-1-methylethylbenzene. Although the iodine produced in these reactions was absorbed with silver powder, the process was found to be irreproducible. The inevitable variations in the mean concentration of free iodine are reflected in the yields of 2,3-dimethyl-2,3-diphenylbutane. The yield of isopropyldiphenyls was greatest, but again variable, with phenyl radicals from iodobenzene. The yield of high-boiling residue varied and was least with iodobenzene as radical source.

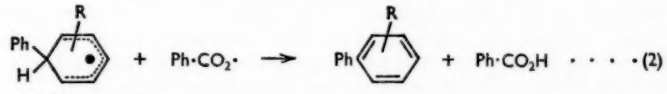
We do not at present propose a full explanation of the variations in ratios of nuclear isomers with the radical source. Several possibilities may, however, be eliminated. First, the ultraviolet radiation itself cannot be a dominating factor since variations in isomer ratios occurred within the group of photolysis experiments. Secondly, the possibility that the " abnormal " ratios involve " hot " phenyl radicals seems unlikely since these ratios are consistent with attack by a rather more selective (*i.e.*, less active) reagent.

A probable mechanism for homolytic aromatic phenylation involves the initial addition of a phenyl radical to the aromatic system, giving a radical analogue of the Wheland intermediate for electrophilic substitution:



. . . . . (1) *

Abstraction of a hydrogen atom from the radical intermediate by, *e.g.*, a benzoyloxy-radical or dibenzoyl peroxide furnishes the diphenyl derivative; *e.g.*:



. . . . (2)

It has recently been shown that the intermediate radicals need not react exclusively in the

* Reaction (1) is written as reversible in view of the lack of contrary evidence.

[4] Foster and Williams, personal communication.

manner of equation (2). For example, Lynch and Pausacker [5] explain the formation of quaterphenyls in terms of dimerization of the intermediate radicals, followed by dehydrogenation. DeTar and Long [6] have identified dihydrodiphenyls among the products from the decomposition of dilute solutions of dibenzoyl peroxide in benzene. Hydrodiphenyls also seem to be formed when diphenylmercury is photolyzed in benzene under nitrogen.[7] Dihydrodiphenyls doubtless arise from disproportionation of the above intermediate radicals, and subsequent dehydrogenation of the former provides an alternative to equation (2) as a route for the production of diphenyls. We consider that under conditions where dehydrogenation is relatively unfavoured, the radical intermediates formed in reaction (1) may reach a higher stationary concentration than is usual. In their subsequent relative tendencies to dimerize or disproportionate, any selectivity between isomers would be reflected in the isomer composition of the substituted diphenyls which are finally isolated.

In the present work, the " abnormal " isomer ratios were observed in experiments with diphenylmercury and tetraphenyl-lead where reactions of type (2) should be relatively unfavoured. With iodobenzene as radical source, the isomer ratios were " normal ": here, free iodine was always present in a varying and irreproducible concentration, despite the addition of silver powder, and would possibly be effective both in dehydrogenating the radical intermediates as in equation (2), and in capturing a proportion of αα-dimethylbenzyl radicals. This suggestion is consistent with the observed evolution of hydrogen iodide, the much higher yield of isopropyldiphenyls, and the variable yields of " dicumyl," when iodobenzene was used as the radical source.

Experimental

The Photolysis Cell.—This was constructed round a Jencon's 1" quartz/borosilicate-glass graded seal. The quartz end of the seal was closed to give a 2" quartz tube. The glass end of the seal was joined co-axially to the bottom of a 100 ml. round-bottomed B.24 " Quickfit " flask. A tube at an upward angle joined to the glass part of the extension served to take a thermometer or thermocouple which was sealed in position with a silicone rubber gland. Two B.14 sockets on the flask at a slight angle to the vertical took a water-condenser which was attached to a mercury-trap at its other end, and a hopper for silver powder. Both radiation and heating were provided by a " Hanovia " S 500 mercury-vapour ultraviolet lamp, which was mounted with the semi-torus of the lamp around the quartz part of the cell, allowing a clearance of 2—3 mm. A removable aluminium sheath fitted between the lamp and the cell, preventing irradiation of the cell contents until the desired temperature had been reached. The lamp and the quartz cell were encased in a ventilated aluminium box, the walls of which were coated with magnesium oxide. During irradiation, the inner quartz surface was continually rubbed with glass wool attached to the axially-impelling stirrer to prevent the deposition of polymer films. The stirrer carried small spikes on its shaft to hold the glass wool in position. The direction of rotation was changed periodically to prevent the glass wool from becoming tightly wound round the stirrer. A shaped polyvinyl chloride gland lubricated with a mixture of petroleum jelly and liquid paraffin formed an air-tight seal between the stirrer and the stirrer guide. A side-arm on the stirrer-guide was used as a nitrogen inlet. The temperature of the cell contents during irradiation was controlled by varying the air-flow from a small cooling-fan which blew air through a duct around the upper parts of the cell extension.

A modified cell with a built-in water jacket has also been used. This enables irradiations to be carried out at temperatures down to 45°. In it, the temperature is very simply adjusted by means of a variable-head device attached to the coolant supply.

Purification of Diphenylmercury.—The product supplied by " Lunevale Products Ltd." contained considerable quantities of halogen. This could not be removed by recrystallization from a variety of solvents. The following procedure proved effective. Crude diphenylmercury (10 g.) was dissolved in the minimum quantity of warm ethanol (*ca.* 150 ml.) and was shaken with moist silver oxide (*ca.* 10 g.) for 30 min. The mixture was then heated under reflux for

[5] Lynch and Pausacker, *Austral. J. Chem.*, 1957, **10**, 165.
[6] DeTar and Long, *J. Amer. Chem. Soc.*, 1958, **80**, 4742.
[7] Blair and Bryce-Smith, unpublished work.

30 min. and filtered while hot. The filtrate was concentrated by evaporation to obtain the diphenylmercury. This was recrystallized from benzene, to give halogen-free material, m. p. 125—126°. This procedure converts phenylmercuric halides into phenylmercuric hydroxide, which is much more soluble in alcohol and benzene.

Preparation of Tetraphenyl-lead.—A solution of phenylmagnesium bromide was prepared in the usual manner from magnesium (7 g.) and bromobenzene (42 g.) in ether (100 ml.). Dry lead chloride (20 g.) was added. Stirring and heating under reflux were continued for about 36 hr., then the mixture was cooled. Water was added, followed by dilute hydrochloric acid. The solid material was washed with water and ether, and finally extracted with benzene in a Soxhlet apparatus, with a heating-tape wound round the extractor unit and so adjusted as to maintain the benzene there just below its b. p. Tetraphenyl-lead (10·8 g.) was extracted. Its m. p. (224—226°) was unchanged after recrystallization from xylene (cf. refs. 8 and 9).

Purification of Iodobenzene.—Commercial material was decolorized by being shaken with aqueous sodium thiosulphate, washed with water, dried ($CaCl_2$), and fractionally distilled under reduced pressure. The fraction boiling at 114°/92 mm. was collected and stored over a little silver powder and calcium chloride.

Isopropylbenzene was purified and stored as previously described.[10]

Photolysis of Diphenylmercury, Tetraphenyl-lead, and Iodobenzene in Isopropylbenzene.—Sufficient diphenylmercury, tetraphenyl-lead or iodobenzene to produce about 2·5 g. of phenyl radicals was irradiated in isopropylbenzene in the cell described for ~6 hr. at 120° ± 10° under nitrogen. With iodobenzene, about 2½ times the theoretical quantity of silver powder was added to absorb the iodine which was set free. Hydrogen iodide was evolved during these photolyses. Sometimes extra silver powder had to be added during the photolyses, so air could not be strictly excluded. After irradiation, the contents of the cell were filtered into a distilling flask. The cell and filter were washed with a little isopropylbenzene, and the washings were added to the mixture in the distilling flask. The mercury liberated from diphenylmercury, and the lead liberated from tetraphenyl-lead, were determined by standard methods to measure the extent of decomposition. The benzene formed during the photolysis was removed with added carbon tetrachloride by fractional distillation and estimated as *m*-dinitrobenzene. The first runnings from this distillation were usually cloudy despite efforts to maintain anhydrous conditions. Most of the isopropylbenzene was removed by fractional distillation. The column was washed down into the flask with light petroleum. Unchanged diphenylmercury was converted into phenylmercuric chloride by heating the residue from the fractional distillation under reflux with a little concentrated hydrochloric acid for 30 min. Insoluble phenylmercuric chloride was filtered off, and the mixture was washed with water and dried. Tetraphenyl-lead remaining unchanged after the photolysis crystallized almost quantitatively, part on cooling of the cell-contents, and the rest as a residue after the fractional distillation. The residual liquid was transferred quantitatively to a small distillation unit, and the distillation continued. Light petroleum, isopropylbenzene, and always some acetophenone,[1] distilled. In the iodobenzene runs the last runnings were added to the forerun of the diphenyl fraction and analyzed for iodine to give an estimate of the iodobenzene remaining unchanged after photolysis and hence of the extent of decomposition. Hydrogen iodide was evolved during the distillation procedure in the iodobenzene runs. The fraction containing the isopropyldiphenyls and 2,3-dimethyl-2,3-diphenylbutane was collected at 75—120°/0·1—0·3 mm. It was always redistilled to remove traces of forerun and terphenyls.* The mixture was analyzed for the four components by the standard infrared spectrographic method described by Hey, Pengilly, and Williams,[1] except that dimethylformamide was used as a solvent in place of nitromethane. 2,3-Dimethyl-2,3-diphenylbutane is sufficiently soluble in dimethylformamide to make unnecessary its prior separation from the mixture of isomeric isopropyldiphenyls.

Control Experiments.—(1) No detectable amount of 2,3-dimethyl-2,3-diphenylbutane was formed when isopropylbenzene was irradiated alone under the conditions of the present experiments. Very small quantities of isopropylfulvenes were formed (cf. ref. 11).

* As judged from iodine analyses, the isopropyldiphenyls obtained by using iodobenzene as radical source consistently contained 1·1—1·3% of iododiphenyls: the latter would be expected to co-distil with isopropyldiphenyls.

[8] Pfeiffer and Truskier, *Ber.*, 1904, **37**, 1125.
[9] Setzer, Leeper, and Gilman, *J. Amer. Chem. Soc.*, 1939, **61**, 1609.
[10] Bryce-Smith, *J.*, 1956, 1603.
[11] Blair and Bryce-Smith, *Proc. Chem. Soc.*, 1957, 287.

XUM

(2) 2,3-Dimethyl-2,3-diphenylbutane was recovered quantitatively after irradiation of a solution in isopropylbenzene.

(3) No detectable amount of 2,3-dimethyl-2,3-diphenylbutane was formed when a solution of iodine in isopropylbenzene was irradiated, although a reaction to give a high-boiling oil did take place.

(4) 2,3-Dimethyl-2,3-diphenylbutane was recovered nearly quantitatively when irradiated in isopropylbenzene containing iodine. Some was probably retained in the oil mentioned in paragraph (3).

The authors thank Professor D. H. Hey, F.R.S., for helpful comments on the manuscript. One of them (J. M. B.) thanks Messrs. Hanovia for a grant. The initial stages of the work were carried out at King's College, London.

THE UNIVERSITY, READING, BERKSHIRE (D. B.-S.).
KING'S COLLEGE, LONDON, W.C.2.
[Present addresses:
(J. M. B.) THE LABORATORY, NEW SCOTLAND YARD, LONDON, S.W.1.
(B. W. P.) 2029, 14TH STREET, CUYUHOGA FALLS, OHIO, U.S.A.]

[*Received, March 18th,* 1959.]

---

646. *Norbornadiene–Metal Complexes and Some Related Compounds.*

By E. W. ABEL, M. A. BENNETT, and G. WILKINSON.

Norbornadiene has given diolefin complexes of silver(I), copper(I), palladium(II), platinum(II), rhodium(I), and ruthenium(II), the last being the first reported olefin complex of ruthenium. The ruthenium–diolefin complex, $C_7H_8RuX_2$ is polymeric with a halogen-bridged structure. Compounds of the type $C_7H_8(p\text{-tol})_2RuX_2$ and py_4RuX_2 are obtained from the polymeric olefin complex with *p*-toluidine and pyridine, respectively. Rhodium(I) complexes of cyclo-octatetraene, the maleic anhydride adduct of cyclo-octatetraene, and the cyclo-octatetraene–(dimethyl acetylenedicarboxylate) adduct, have been made; they are binuclear with the general formula $(diene)_2Rh_2Cl_2$.

IN this paper we report the formation of a series of metal–olefin complexes obtained from the hydrocarbon norbornadiene (bicyclo[2,2,1]hepta-2,5-diene) (I). The most stable olefin co-ordination complexes previously known have been those formed by cyclo-octa-1,5-diene,[1] which was used by Chatt and his co-workers to determine the limits of olefin–metal complex formation in the Periodic Table. The farthest point reached to the left of the Table by these workers was rhodium. It was reported that iridium, ruthenium, and osmium did not form complexes with the octadiene.[1] We have now been able to move one Group further to the left of the Periodic Table by the formation of the norbornadiene-ruthenium dihalides; a norbornadiene–iron compound of a different type, $C_7H_8Fe(CO)_3$, has also been prepared [2] and will be described in more detail subsequently. Although no unconjugated olefin complex of a metal to the left of the iron Group has been made directly from the olefin, the rhenium–olefin complexes, $\pi\text{-}C_5H_5Re(CO)_2C_5H_6$ and $\pi\text{-}C_5H_5Re(CO)_2C_5H_8$, have been obtained indirectly.[3]

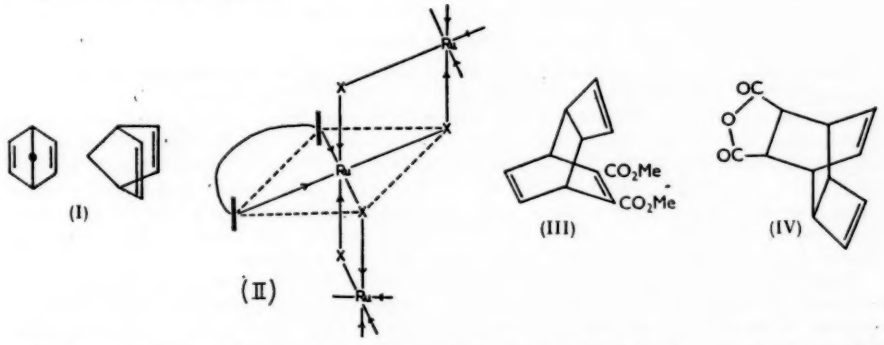
With silver nitrate, norbornadiene produced the compound $C_7H_8(AgNO_3)_2$ as white crystals; this is in contrast to the 1 : 1 metal–diene complex formed by cyclo-octa-1,5-diene.[4] Recently, however, it was reported [5] that norbornadiene forms a 1 : 1 silver

[1] Chatt and Venanzi, *J.*, 1957, 4735, and papers quoted therein.
[2] Burton, Green, Abel, and Wilkinson, *Chem. and Ind.*, 1958, 1592.
[3] Green and Wilkinson, *J.*, 1958, 4314.
[4] Jones, *J.*, 1954, 312.
[5] Traynham and Olechowski, *J. Amer. Chem. Soc.*, 1959, **81**, 571.

complex; the product was not crystallised in this case. It appears that the stoicheiometry of the silver nitrate–cyclopolyolefin compounds may vary considerably, depending on the conditions of preparation.[6] Anhydrous cupric bromide and norbornadiene in ethanol formed the Cu(I) compound, $C_7H_8(CuBr)_2$, analogous to the above silver nitrate complex.

The norbornadiene complexes of rhodium(I), $(C_7H_8)_2Rh_2Cl_2$, palladium(II), $C_7H_8PdCl_2$, and platinum(II), $C_7H_8PtCl_2$, appear to be analogous to the corresponding compounds of cyclo-octa-1,5-diene.[1,7,8] Thus, it is reasonable to assume that the metal in these compounds has a planar 4-co-ordinate dsp^2-hybridized state. The compounds are insoluble in water, but soluble in chloroform, acetic acid, and other organic solvents.

Norbornadieneruthenium dichloride, $C_7H_8RuCl_2$, was made by direct reaction between ruthenium trichloride and the hydrocarbon in ethanol; the corresponding bromide was formed similarly. If, in these compounds, the metal was regarded as having a co-ordination number of four, both the planar (dsp^2) and the tetrahedral (sp^3) form would have to be paramagnetic. The compounds are, however, diamagnetic, and in view of the virtually unknown co-ordination number of four for ruthenium, the metal undoubtedly attains its usual co-ordination number of six by the formation of the halogen-bridged structure (II; X = halogen). This structure resembles that proposed by Irving [9] for ruthenium carbonyl iodide, in having halogen bridges; although the relative disposition of the carbonyl groups was not explicitly stated, the diagram given indicates a *trans*-position for the two carbonyl groups. The infrared spectrum of the compound shows two very strong C–O stretching modes at 1995 and 2050 cm.$^{-1}$, so that a *cis*-configuration appears more likely, although solid-state interaction in the *trans*-form, which could lead to splitting of the expected single frequency, cannot be rigorously excluded. However, in the above diolefin complex, the olefin groups must necessarily be mutually *cis*. This results in a " curling " spiral chain structure for $C_7H_8RuX_2$. Such a spiral chain structure with *cis*-carbonyl groups is also a more likely alternative structure for the carbonyl iodide. The virtual insolubility of $C_7H_8RuX_2$, as well as $(CO)_2RuX_2$, in all solvents supports the polymeric structure for these compounds.



p-Toluidine caused fission of the halogen bridge in $[C_7H_8RuX_2]_n$ to give the corresponding bis-*p*-toluidinenorbornadieneruthenium dihalides:

$$(C_7H_8RuX_2)_n + 2n(p\text{-tol}) = nC_7H_8(p\text{-tol})_2RuX_2$$

Pyridine not only caused fission of the halogen bridge in the diolefin polymer but also displaced the diolefin to give the monomeric tetrapyridineruthenium dihalides; other reactions of this type will be reported later.

[6] Cope and Hochstein, *J. Amer. Chem. Soc.*, 1950, **72**, 2515.
[7] Chatt, Vallarino, and Venanzi, *J.*, 1957, 2496.
[8] *Idem*, *J.*, 1957, 3413.
[9] Irving, *J.*, 1956, 2879.

XUM

Rhodium trichloride in ethanol solution has proved particularly reactive towards compounds having a chelating diolefin group, and compounds of general formula $L_2Rh_2Cl_2$ have been isolated where L is cyclo-octatetraene, the cyclo-octatetraene–(dimethyl acetylenedicarboxylate) adduct (III) and cyclo-octatetraene–maleic anhydride adduct (IV). The rhodium chloride complexes of the first two of these have been shown to be dimeric, but the low solubility of the other product prevented a direct determination. These three compounds may be regarded as analogous to the octa-1,5-diene and norbornadiene complexes of rhodium. All three compounds are stable in the crystalline form, and in solution, despite a previous report [1] that cyclo-octatetraenerhodium chloride was too unstable to be purified.

It is interesting that in the adduct (III) there are three olefinic bonds and it is not possible at this stage to say definitely which pair is being used as a chelating diolefin. This problem is however being investigated as part of a programme of nuclear magnetic resonance studies on the above and other olefin complexes, results of which will be communicated later.

We may note finally that norbornadiene is the only chelating diolefin known so far which gives complexes with the elements at the heavy ends of the transitional series as well as with iron and ruthenium. Whilst norbornadiene has been shown [10] to behave as a quasi-conjugated system, undergoing, for example, the Diels–Alder addition with maleic anhydride, it is not certain yet whether this behaviour is essential for binding to iron or ruthenium although only conjugated olefins have previously been known to form complexes with iron.[11] Indeed, the nuclear magnetic resonance spectra of the norbornadiene–iron and –rhodium compounds [12] do not show the separation of the olefinic proton resonances into high- and low-field groups observed for conjugated olefin–metal complexes.[12] The distance between the double bonds in the diolefins may be the important factor, and scale models show the distance in norbornadiene to be about 10% shorter (2·5 Å) than in cyclo-octa-1,5-diene (2·8 Å); this shortening would obviously allow better overlap between the metal hybrid orbitals and the π-electron density in the olefin.

Experimental

Microanalyses and molecular-weight measurements were by the Microanalytical Laboratory, Imperial College. Magnetic measurements were made by the Gouy method.

Norbornadienedi(silver Nitrate).—Silver nitrate (1·36 g.) in water (10 c.c.) was added to the hydrocarbon (3 ml.) and shaken for 5 min. The white solid complex was filtered off and recrystallised from ethanol, to give the pure *product* (0·95 g.) [Found: C, 19·4; H, 2·4; Ag, 50·2. $C_7H_8(AgNO_3)_2$ requires C, 19·5; H, 1·9; Ag, 50·0%]. The white crystals decompose in water, giving a strong smell of norbornadiene; they also decompose when kept in the air or warmed. The complex is soluble in warm methanol, ethanol, carbon tetrachloride, chloroform, and benzene but is almost insoluble in acetone, ether, and light petroleum.

Norbornadienedi(cuprous Bromide).—Anhydrous cupric bromide (2·6 g.) in ethanol 30 c.c.) was shaken for 5 min. with norbornadiene (5 c.c.). After the white crystalline product had been removed by filtration it was washed with ethanol (5 c.c.) and ether (5 c.c.). *Norbornadienedi(cuprous bromide)* (1·4 g.) [Found: C, 19·8; H, 2·6; Cu, 32·8. $C_7H_8(CuBr)_2$ requires C, 22·2; H, 2·1; Cu, 33·5%] remained as fine white crystals which slowly become green in air. The complex readily lost norbornadiene at reduced pressure to leave cuprous bromide, and was decomposed in water to give cuprous oxide. It is practically insoluble in all common organic solvents.

Although the analytical figures are not satisfactory in spite of the formation of well-defined crystals, it may be noted that many other copper–olefin complexes have been reported to be unstable and in some cases analyses for carbon and hydrogen have not even been attempted (cf. ref. 13).

[10] Ullman, *Chem. and Ind.*, 1958, 1173.
[11] Hallam and Pauson, *J.*, 1958, 642.
[12] Green, Pratt, and Wilkinson, *J.*, 1959, in the press.
[13] Slade and Jonassen, *J. Amer. Chem. Soc.*, 1957, **79**, 1277.

Interaction of Platinic Chloride and Norbornadiene.—The chloride (1 g.) in glacial acetic acid (10 c.c.) was shaken for 15 min. with norbornadiene (2 c.c.). The brown solid was filtered off and a further quantity obtained by addition of light petroleum to the mother-liquor. Recrystallization from acetic acid gave *norbornadieneplatinum dichloride* (0·4 g.) (Found: C, 23·8; H, 2·4; Pt, 54·6; Cl, 19·0. $C_7H_8PtCl_2$ requires C, 23·5; H, 2·3; Pt, 54·5; Cl, 19·8%) as fine white crystals, decomp. 230—280°, somewhat soluble in acetic acid, chloroform, and acetone.

Norbornadienepalladium Dichloride.—Dibenzonitrilepalladium dichloride [14] (1·1 g.) in chloroform (35 c.c.) was shaken with norbornadiene (4 c.c.) and set aside for 1 hr. The yellow deposit was filtered off and washed with chloroform and light petroleum. After recrystallization from acetic acid, the *product* was washed with methanol and acetone and dried in a vacuum. It formed yellow needles (0·58 g.), decomp. 190—200° (Found: C, 31·4; H, 3·6. $C_7H_8PdCl_2$ requires C, 31·2; H, 3·0%).

Norbornadieneruthenium Dichloride.—Ruthenium "trichloride" (1·03 g.) (commercial mixture of hydrated tri- and tetra-chloride) was dissolved in ethanol (40 c.c.), and the solution was centrifuged to remove insoluble material. The red-brown solution was shaken with norbornadiene (4 c.c.) and kept for 25 hr. The red product was washed repeatedly with acetone to remove ruthenium chlorides. The final *product* (0·6 g.) (Found: C, 31·6; H, 3·9; Cl, 27·5. $C_7H_8RuCl_2$ requires C, 31·8; H, 3·1; Cl, 26·8%) was diamagnetic and insoluble in water and all organic solvents.

Norbornadieneruthenium Dibromide.—Ruthenium "trichloride" (1·1 g.) was dissolved in acetone (40 c.c.), and insoluble material removed as above. Then lithium bromide (4 g.) was added and the solution was filtered and added to norbornadiene (4 c.c.) and set aside for 24 hr. The precipitated complex, after repeated washing with acetone, was dried in a vacuum, to give the pure *product* (0·6 g.) (Found: C, 23·2; H, 2·8. $C_7H_8RuBr_2$ requires C, 23·8; H, 2·3%) as a dark brown solid insoluble in all solvents.

Interaction of Norbornadieneruthenium Dichloride and Pyridine.—The dichloride (0·39 g.) in pyridine (15 c.c.) was heated at 120° for 45 min. Cooling the resultant red solution gave red crystals. Recrystallization from chloroform–light petroleum gave pure tetrapyridineruthenium dichloride (0·3 g.), m. p. 220—224° (decomp.) [Found: C, 49·4; H, 4·3; N, 11·4; Cl, 14·8%; *M*, 487 (ebullioscopic in benzene). Calc. for $C_{20}H_{20}Cl_2N_4Ru$: C, 49·1; H, 4·3; N, 11·5; Cl, 14·5%; *M*, 489].

Interaction of Norbornadieneruthenium Dihalides and p-*Toluidine.*—The dichloride (0·29 g.) was fused with *p*-toluidine (0·8 g.) and kept at 100° for 30 min. After being cooled, the red solid residue was washed with ether and dichloromethane, to leave yellow crystals which after vacuum-drying gave *norbornadienedi-*(p-*toluidine*)*ruthenium dichloride* (0·2 g.), decomp. >80° (Found: C, 53·1; H, 5·4; N, 6·2; Cl, 14·7. $C_{21}H_{26}N_2Cl_2Ru$ requires C, 52·6; H, 5·5; N, 5·9; Cl, 14·8%), soluble in chloroform.

In a similar manner *norbornadienedi-*(p-*toluidine*)*ruthenium dibromide*, decomp. >80° (Found: C, 45·0; H, 5·1; N, 4·9; Br, 27·9. $C_{21}H_{26}N_2Br_2Ru$ requires C, 44·4; H, 4·6; N, 4·9; Br, 28·2%), was prepared from $C_7H_8RuBr_2$ and *p*-toluidine.

Cyclo-octatetraenerhodium(I) *Chloride.*—Rhodium "trichloride" (1·4 g.) and cyclo-octatetraene (5 c.c.) in ethanol (50 c.c.) were kept at room temperature for 1 month. The fine orange crystals deposited were washed with ethanol and ether and dried in a vacuum, to leave pure *cyclo-octatetraenerhodium chloride* (0·2 g.), m. p. 140—145° (decomp.) [Found: C, 40·0; H, 3·9; Cl, 13·9%; *M*, 476 (ebullioscopic in benzene). $(C_8H_8RhCl)_2$ requires C, 39·6; H, 3·3; Cl, 14·6%; *M*, 485]. The complex is easily soluble in benzene, chloroform, and methylene dichloride to give yellow solutions which do not noticeably decompose when warmed; it is insoluble in light petroleum, ether, and ethanol.

Norbornadienerhodium(I) *Chloride.*—Rhodium trichloride (0·7 g.) and norbornadiene (2 c.c.) in aqueous ethanol (10 c.c.) were shaken together for 2 days. The yellow deposit was recrystallized from hot chloroform–light petroleum, to give pure *norbornadienerhodium chloride* (0·62 g.), decomp. 240° [Found: C, 37·3; H, 3·7; Rh, 45·3; Cl, 15·5%; *M*, 481 (ebullioscopic in benzene). $(C_7H_8RhCl)_2$ requires C, 36·5; H, 3·5; Rh, 44·6; Cl, 15·4%; *M*, 462], as fine yellow crystals, soluble in chloroform and benzene, but almost insoluble in ether and light petroleum.

Interaction of the Maleic Anhydride Adduct of Cyclo-octatetraene with Rhodium Trichloride.—The adduct (tricyclo[4,2,2,$0^{2,5}$]deca-3,9-diene-7,8-dicarboxylic anhydride) (0·75 g.) and trichloride (0·5 g.) in ethanol (25 c.c.) were heated at 70° for 2 hr. The yellow crystals deposited

[14] Kharasch, Seyler, and Mayo, *J. Amer. Chem. Soc.*, 1938, **60**, 882.

XUM

were washed with alcohol and ether and dried in a vacuum, to leave *adduct–rhodium*(I) *chloride* (0·35 g.), decomp. 190° (Found: C, 42·0; H, 4·0; O, 14·7. $C_{12}H_8O_3RhCl$ requires C, 42·3; H, 3·0; O, 14·1%). Although direct measurement of the molecular weight of this compound was not possible owing to its low solubility, its diamagnetism suggests the dimeric structure analogous to all the other diolefin–rhodium chlorides described.

Interaction of Cyclo-octatetraene–(Dimethyl Acetylenedicarboxylate) Adduct and Rhodium Trichloride.—The adduct (dimethyl tricyclo[4,2,2,$0^{2,5}$]deca-3,7,9-triene-7,8-dicarboxylate) (1 g.) and trichloride (1 g.) in ethanol (10 c.c.) were heated at 70° for 1 hr. After cooling, the green-yellow crystals deposited were washed with cold alcohol and ether, and dried in a vacuum, to leave pale-green crystals of the *adduct–rhodium*(I) *chloride* [Found: C, 43·5; H, 3·9; Rh, 27·3; Cl, 9·4; O, 16·5%; *M*, 748 (ebullioscopic in benzene). $(C_{14}H_{14}O_4RhCl)_2$ requires C, 43·6; H, 3·6; Rh, 26·8; Cl, 9·4; O, 16·6%; *M*, 770], which are soluble in chloroform and benzene but only very slightly soluble in ether and light petroleum.

Infrared Spectra.—Spectra were measured on a Perkin-Elmer Model 21 spectrophotometer.

Norbornadiene in CCl_4 *and* CS_2: 3080(s), 2960(vs), 2880(s), 1646(m), 1452(ms), 1335(ms), 1310(vs), 1271(m), 1229(s), 1206(s), 1150(s), 1105(ms), 1063(m), 1016(m), 1016(m), 935(s), 911(s), 885(sh), 870(vs), 795(sh), 745(sh), 715(vs), 650(s).

$(C_7H_8)_2Rh_2Cl_2$ *in* CS_2: 3060(m), 3000(m), 2960(m), 2920(m), 2855(m), 1307(s), 1171(m), 1157(w), 1068(w), 1029(w), 995(w), 932(m) 882(m), 721(w), 680(s), 630(s).

$C_7H_8PtCl_2$ *in Nujol and hexachlorobutadiene mulls*: 3060(ms), 2930(w), 2880(w), 1436(m), 1412(w), 1371(sh), 1315—1310(split peak, s), 1262(vw), 1250(vw), 1187(m), 1162(vw), 1120—1025(vw, broad), 985(m), 978(m), 954(w), 939(w), 909(w), 880(vw), 833(vw), 822(w), 800(w), 775(w), 720(s, broad, rising).

$C_7H_8PdCl_2$ *in Nujol mull* (3000 cm.$^{-1}$ region omitted): 1410(m), 1305(m), 1230(w), 1180(m), 1160—1108(broad, w), 970(m), 941(m), 900(m), 880(w), 828(w), 797(sh), 792(m), 765(w), 718(w).

$C_7H_8,2AgNO_3$ *in Nujol and hexachlorobutadiene mulls*: 3020(w), 2960(w), 2885(w), 1470(m), 1385(v, broad, s), 1325(s), 1310(s), 1310(s), 1243(m), 1189(m), 1046(m), 1014(w), 969(m), 950(vw), 929(m), 890(w), 877(w), 808(m), 795(w), 790(m), 760(w), 725(ms).

$C_7H_8,2CuBr$ *in Nujol and hexachlorobutadiene mulls*: 3027(vw), 3000(vw), 2930(m), 2860(w), 1471(w), 1453(m), 1310(ms), 1265(w), 1245(vw), 1234(w), 1180—1080(broad,w), 1050(vw), 993(m), 976(m), 950(w), 938(w), 918(ms), 889(w), 867(w), 777(w), 765(w), 739(m), 719(m).

$C_7H_8RuCl_2$ *in Nujol and hexachlorobutadiene mulls*: 3098(w), 3098(w), 3025(m), 2975(sh), 2940(m), flat shoulder from 2863 to 2900, 1420(vw), 1409 (vw), 1310(m), 1258(vw), 1240(vw), 1180(w), 1160(w), 1085(w), 1035(w), 1000(vw), 941(w), 888(w), 863(w), 805(w), 779(w).

$C_7H_8RuBr_2$ *in Nujol and hexachlorobutadiene mulls*: 3025(w), 2960(m), 2915(vw), 2880(m), 1438(w), 1410(m), 1397(m), 1301(s), 1258(vw), 1225(vw), 1170(m), 1150(sh), 1078(w), 1025(vw), 935(w), 884(w), 858(w), 800(m), 775(m), 718(m).

$C_7H_8Ru(p\text{-tol})_2Cl_2$ *in Nujol mull below* 1400 *cm.*$^{-1}$ *only*: 1305(m), 1179(m), 1118(s), 1105(sh), 1040(w), 946(m), 840(m), 816(s), 799(m), 713(m).

The authors thank Professor R. C. Cookson and Dr. J. D. Hudec for gifts of compounds, the Shell Petroleum Company Ltd. for a gift of norbornadiene, and Johnson, Matthey and Co. Ltd. for the loan of platinum-metal halides. The financial support (E. W. A. and M. A. B.) of the Ethyl Corporation is gratefully acknowledged.

Inorganic Chemistry Research Laboratories,
Imperial College of Science and Technology,
London, S.W.7.

[*Received, March 16th,* 1959.]

647. *The Relative Stabilising Influences of Substituents on Free Alkyl Radicals. Part VI.*[1] *The Cleavage of Substituted Dibenzyl Ethers by Grignard Reagents in the Presence of Cobaltous Chloride.*

By R. L. Huang and Surinder Singh.

From the cleavage of nine mono- and seven di-substituted dibenzyl ethers by the cobalt-catalysed Grignard reaction, the following scales of stabilising influence on free benzyl radicals have been established: *m*- and *p*-Me and -Cl, *p*-Bu^t, -OMe, and -Ph > H; *p*-Bu^t > *p*-Me ~ *p*-Cl > *p*-OMe > H; *m*- and *p*-Me > *m*-Cl ≥ *p*-OMe > H; and *p*-Me > *p*-Ph > H. The results are explained in terms of radical-stabilisation by homomesomerism, in conjunction with polar effects, due to the substituents.

The cleavage of dibenzyl ether by Grignard reagents in the presence of cobaltous chloride proceeds *via* the radical ·CHPh·O·CH_2Ph which disproportionates to benzaldehyde and free benzyl, and these in turn are reduced, respectively, to benzyl alcohol and toluene.[2] By studying the direction of fission of monosubstituted dibenzyl ethers, it was possible to compare the relative stabilising influences of the substituents, with respect to hydrogen, on the intermediate benzyl radical. We now report (*a*) further work on the monosubstituted ethers, and (*b*) the cleavage of disubstituted ethers R·C_6H_4·CH_2·O·CH_2·C_6H_4R′ in which comparison is made of the stabilising effects of R and R′.

The method of cleavage previously reported[2] (isopropylmagnesium bromide and cobaltous chloride) was used. For the monosubstituted ethers, the technique of isolating, in a 50% or higher yield, one of the benzyl alcohols to determine the main course of fission was adopted. For the disubstituted ethers, however, a more quantitative approach was attempted wherever possible, involving estimation of the molar ratio of the two benzyl alcohols formed, each of the minor products being identified, but not all quantitatively isolated. In most cases it was possible, from the alcohols produced, to account for 80—90% of the ether which reacted.

Experimental

Synthesis of Ethers.—The ethers (all new compounds) were prepared as previously described, and are listed in Table 1.

Table 1. *Synthesis of dibenzyl ethers,* R·C_6H_4·CH_2·O·CH_2·C_6H_4R′.

			X·C_6H_4·CH_2Hal				Found (%)			Reqd. (%)	
No.	R	R′	X	Hal	Yield (%)	B. p./mm.	n_D (temp.)	C	H	Formula	C	H
1	H	*m*-Cl	*m*-Cl	Br	73	112—116°/0·2	1·5694(22°)			$C_{14}H_{13}OCl$ [a]		
2	H	*o*-Cl	*o*-Cl	Br	67	130°/0·4	1·5682(23·5°)	72·7	5·6	$C_{14}H_{13}OCl$	72·4	5·6
3	H	*o*-Me	*o*-Me	Br	81	117°/0·2	1·5588(24°)	84·4	7·7	$C_{15}H_{16}O$	84·9	7·6
4	*p*-Me	*p*-Cl	*p*-Me	Br	85	m. p. 63—64°	—	72·5	6·2	$C_{15}H_{15}OCl$	73·0	6·1
5	*p*-Me	*m*-Cl	*m*-Cl	Br	85	110—112°/0·1	1·5632(23°)	73·3	6·3	$C_{15}H_{15}OCl$ [b]	73·0	6·1
6	*p*-Me	*p*-Bu^t	*p*-Bu^t	Br	81	124—128°/0·2	1·5383(25°)	85·0	8·8	$C_{19}H_{24}O$	85·1	9·0
7	*p*-Me	*p*-Ph	*p*-Ph	Cl	86	m. p. 62—63°		87·6	7·1	$C_{21}H_{20}O$	87·5	6·9
8	*m*-Me	*m*-Cl	*m*-Cl	Br	91	124—127°/0·1	1·5637(24°)	73·0	6·1	$C_{15}H_{15}OCl$	73·0	6·1
9	*p*-Cl	*p*-OMe	*p*-Cl	Cl	87	164—166°/0·3	1·5692(23°)			$C_{15}H_{15}O_2Cl$ [c]		
10	*m*-Cl	*p*-OMe	*m*-Cl	Br	85	164—168°/0·3	1·5693(22°)			$C_{15}H_{15}O_2Cl$ [d]		

[a] Found: Cl, 15·3. Reqd.: Cl, 15·3%. [b] Found: Cl, 14·0. Reqd.: Cl, 14·4%. [c] Found: Cl, 13·0. Reqd.: Cl, 13·5%. [d] Found: OMe, 12·3. Reqd.: OMe, 11·8%.

[1] Part V, Huang and Williams, *J.*, 1958, 2637.
[2] Huang and Si-Hoe, *J.*, 1957, 3988.

XUM

3-Chlorodibenzyl Ether.—(*a*) [3] The cleavage products from this ether (21·2 g., 0·086 mole) were fractionally distilled to give (i) a liquid, b. p. 54—60°/760 mm. (2 g.), probably 2 : 3-dimethylbutane; (ii) toluene, b. p. 109—111°/760 mm. (2·8 g.), $n_D^{22·5}$ 1·4908, oxidised by alkaline potassium permanganate to benzoic acid, m. p. and mixed m. p. 121°; (iii) benzyl alcohol, b. p. 64—66/0·5 mm. (2·0 g., 0·0185 mole), $n_D^{23·5}$ 1·5378 [3 : 5-dinitrobenzoate, m. p. and mixed m. p. 112°] (lit., n_D^{20} 1·5395, m. p. 112°); (iv) 3-chlorobenzyl alcohol, b. p. 84— 85°/0·5 mm. (6·35 g., 0·045 mole, 52% yield), n_D^{24} 1·5513 (Found: Cl, 24·5. Calc. for C_7H_7OCl: Cl, 24·9%), [3,5-dinitrobenzoate, needles (from light petroleum), m. p. 97—98° (Found: O, 28·7. $C_{14}H_9O_6N_2Cl$ requires O, 28·6%)].

(*b*) The cleavage products from the ether (24·0 g., 0·10 mole) on distillation gave the following fractions: (i) Toluene, b. p. 109—110°/761 mm., n_D^{21} 1·4942 (4·35 g., 0·047 mole). (ii) A mixture of benzyl and 3-chlorobenzyl alcohol, b. p. 58—66°/0·5 mm., $n_D^{21·5}$ 1·5362 (3·30 g.), the chlorine content of which (Found: Cl, 7·9%) indicated that it consisted of 0·021 mole of benzyl alcohol and 0·0074 mole of 3-chlorobenzyl alcohol. The phenylurethane prepared from the mixture had m. p. 77—78°, alone or mixed with that prepared from benzyl alcohol. (iii) A mixture (8·57 g.), b. p. 70—74°/0·5 mm., 233—234°/760 mm., $n_D^{21·5}$ 1·5515 (Found: Cl, 23·0%), containing 0·0061 and 0·055 mole, respectively, of the same alcohols. It gave the phenylurethane of 3-chlorobenzyl alcohol, needles (from light petroleum), m. p. 92—93° (Found: N, 5·25. $C_{14}H_{12}O_2NCl$ requires N, 5·4%). (iv) A small residue (bath up to 140°/0·5 mm.). The products therefore consisted of toluene (0·047 mole), benzyl alcohol (0·027 mole), and 3-chlorobenzyl alcohol (0·063 mole, 63%).

2-Chlorodibenzyl Ether.[3]—The fission products from this ether (34 g., 0·15 mole) were fractionated to give (i) toluene (4·2 g., 0·046 mole), (ii) benzyl alcohol (2·3 g., 0·029 mole), (iii) 2-chlorobenzyl alcohol, b. p. 80°/0·5 mm. (8·2 g., 0·058 mole), needles (from benzene), m. p. 73—74° (Mettler [4] reports m. p. 72°), and (iv) a residue (1·3 g.).

2-Methyldibenzyl Ether.[3]—This ether (30 g., 0·14 mole) on cleavage gave (i) toluene (4·75 g., 0·052 mole), (ii) *o*-xylene, with some toluene, b. p. 143—144°/760 mm., n_D^{25} 1·4985 (2·6 g., 0·025 mole), (iii) benzyl alcohol (3·5 g., 0·032 mole), (iv) 2-methylbenzyl alcohol, b. p. 62—65°/0·2 mm. (9·3 g., 0·076 mole, 54%), m. p. 34—35° (lit., m. p. 36°) (Found: C, 78·8; H, 8·1. Calc. for $C_8H_{10}O$: C, 78·7; H, 8·2%) [*p*-nitrobenzoate, m. p. 99—100° (lit., m. p. 100—101°)], and (v) a residue (0·5 g.).

4-Chloro-4'-methyldibenzyl Ether.—This (19·5 g., 0·080 mole) yielded the following products:—(i) A mixture of toluene and *p*-xylene, b. p. 64—74°/100 mm., 116—120°/760 mm. (1·4 g.), $n_D^{22·5}$ 1·4920. A portion (0·5 g.) was oxidised with alkaline potassium permanganate and the mixture of products extracted with chloroform to give benzoic acid, m. p. and mixed m. p. 122° (0·34 g.), and with ether to give terephthalic acid, m. p. >300° (sublimes) (0·09 g.) (dimethyl ester, m. p. and mixed m. p. 141°). (ii) *p*-Xylene, b. p. 74—82°/100 mm., 135—136°/760 mm. (1·4 g., 0·013 mole), n_D^{23} 1·4932 (2,3,5-trinitro-derivative, m. p. and mixed m. p. 139°) (lit., b. p. 137°/760 mm., n_D^{21} 1·5004). (iii) *4-Methylbenzyl alcohol*, b. p. 70—75°/0·3 mm. (1·63 g., 0·013 mole), m. p. and mixed m. p. 54—55° (from light petroleum) (lit.,[5] m. p. 57—58°). To ascertain the absence of benzyl alcohol the mother-liquors from the above recrystallisations were concentrated and the residue was treated with phenyl isocyanate, giving a crude urethane (1·55 g.), recrystallisation of which from ligroin gave two crops (1·3 g.) of the phenylurethane of 4-methylbenzyl alcohol, m. p. and mixed m. p. 74—76° (mixed m. p. with benzylphenylurethane, 55—58°). (iv) A mixture of 4-methyl- and 4-chloro-benzyl alcohol, b. p. 75—82°/0·3 mm. (3·97 g.), which was redistilled (see below). (v) 4-Chlorobenzyl alcohol, b. p. 84—86°/0·3 mm., needles (from cyclohexane), m. p. and mixed m. p. 71—72° (1·47 g., 0·010 mole). (vi) Unchanged ether (4·65 g.). The cyclohexane mother-liquor from fraction (v) was concentrated, combined with fraction (iv), and redistilled, giving (*a*) material, b. p. 68—70°/0·3 mm. (0·15 g.), probably mainly 4-methylbenzyl alcohol; (*b*) a mixture, b. p. 70—74°/0·3 mm. (2·2 g.) (Found: Cl, 8·6%) of 4-methyl- (1·44 g.), and 4-chloro-benzyl alcohol (0·76 g.); (*c*) a mixture, b. p. 78—82°/0·3 mm. (1·2 g.) (Found: Cl, 20·7%) of the same alcohols (0·20 and 0·99 g., respectively); and (*d*) a residue of 4-chlorobenzyl alcohol (*ca.* 0·45 g.). Thus the main products from the ether which reacted (14·8 g., 0·060 mole) were 4-methyl- (3·4 g., 0·028 mole) and 4-chlorobenzyl alcohol (3·7 g., 0·026 mole).

[3] We thank Miss S. Si-Hoe for collaboration in this experiment.
[4] Mettler, *Ber.*, 1905, **38**, 1750.
[5] Mozingo and Folkers, *J. Amer. Chem. Soc.*, 1948, **70**, 230.

3-*Chloro*-4'-*methyldibenzyl Ether*.—This ether (25 g., 0·10 mole) gave products which were fractionated as follows: (i) Material, b. p. 40°/100 mm. (0·6 g.), mainly 2,3-dimethylbutane, b. p. 50—60°/760 mm., and traces of toluene, b. p. 110°/760 mm., n_D^{23} 1·4905. (ii) A mixture of toluene and *p*-xylene, b. p. 80°/100 mm., 116—118°/761 mm. (1·5 g.), n_D^{24} 1·4850, a portion (0·50 g.) of which on oxidation with alkaline potassium permanganate yielded benzoic acid (0·29 g.), and terephthalic acid (0·10 g.) (identified as the dimethyl ester). (iii) *p*-Xylene, b. p. 50—60°/30 mm. (1·5 g.), which was redistilled, (b. p. 130—136°/760 mm., n_D^{26} 1·4918; 1·0 g.) (2,3,5-trinitro-derivative, m. p. and mixed m. p. 139°). (iv) Material, b. p. 72—76°/1 mm., 218°/760 mm., n_D^{27} 1·5278 (1·69 g.), whose b. p. and chlorine content (Found: Cl, 2·2, 1·9%) indicated that it was a mixture of 4-chloro- (0·14 g.) and 4-methyl-benzyl alcohol (1·55 g.). It gave the phenylurethane of the latter alcohol (m. p. and mixed m. p. 79—80°). (v) A mixture, b. p. 76—80°/1 mm., m. p. 51—54° (3·08 g.) (Found: Cl, 3·4; 3·4%), of 4-chloro- (0·42 g.) and 4-methyl-benzyl alcohol (2·66 g.). It gave the phenylurethane of the latter alcohol. (vi) A mixture, b. p. 83—86°/1 mm., n_D^{27} 1·5416 (3·44 g.) (Found: Cl, 13·9, 13·9%), of 3-chloro- (1·92 g.) and 4-methyl-benzyl alcohol (1·52 g.), a portion (0·52 g.) of which with alkaline potassium permanganate yielded *m*-chlorobenzoic acid, m. p. and mixed m. p. 157—158° (0·53 g.), and terephthalic acid (0·15 g.) identified as previously. The mixture gave a phenylurethane which after five recrystallisations from ligroin had m. p. 92—93°, alone or mixed with that prepared from 3-chlorobenzyl alcohol. (vii) Unchanged ether, b. p. 114—116°/0·1 mm. (7·84 g., 0·032 mole). The main products from the ether cleaved (0·070 mole) are thus *p*-xylene (1·5 g., 0·013 mole) and 4-methyl- (5·73 g., 0·047 mole) and 3-chloro-benzyl alcohol (2·50 g., 0·017 mole).

4-*Methyl*-4'-*t*-*butyldibenzyl Ether*.—This ether (30 g., 0·11 mole) gave the following fission products: (i) *p*-Xylene, b. p. 72—74/45 mm., 138—139°/760 mm., $n_D^{26·5}$ 1·4920 (6·25 g., 0·059 mole) (2,3,5-trinitro derivative, m. p. and mixed m. p. 139—140°; and oxidised to terephthalic acid). (ii) *p*-t-Butyltoluene, mixed with some *p*-xylene, b. p. 178°/760 mm., $n_D^{24·5}$ 1·4889 (1·55 g.), a portion (0·52 g.) of which gave *p*-t-butylbenzoic acid, m. p. and mixed m. p. 164° (0·29 g.), and terephthalic acid (0·12 g.). (iii) Material, b. p. 92—96°/1 mm., 248°/759 mm. (5·10 g.), n_D^{27} 1·5145, consisting mainly of 4-t-butylbenzyl alcohol. A sample (0·55 g.) was oxidised to *p*-t-butylbenzoic (0·47 g.) and terephthalic acid (0·016 g.). (iv) 4-t-Butylbenzyl alcohol, b. p. 96—100°/1 mm., 254°/760 mm. (7·85 g., 0·048 mole), n_D^{27} 1·5150, a portion (0·53 g.) of which afforded *p*-t-butylbenzoic acid (0·49 g.) only. The 3,5-dinitrobenzoate, needles (from ligroin), melted at 162° (Found: C, 60·4; H, 5·0. $C_{18}H_{18}O_6N_2$ requires C, 60·3; H, 5·0%). (v) Uncleaved ether (5·6 g., 0·021 mole). The main cleavage products were thus *p*-xylene (6·25 g., 0·059 mole) and 4-t-butylbenzyl alcohol (12·2 g., 0·074 mole).

3-*Chloro*-3'-*methyldibenzyl Ether*.—Fractionation of the cleavage products from this ether (25 g., 0·10 mole) gave the following: (i) *m*-Xylene mixed with some toluene, b. p. 124—130°/760 mm., n_D^{25} 1·4920 (1·80 g.). A sample (0·50 g.) yielded benzoic (0·063 g.) and isophthalic acid (0·42 g.) (dimethyl ester, m. p. and mixed m. p. 64—65°). (ii) *m*-Xylene, b. p. 139—140°/760 mm., n_D^{25} 1·4930 (1·20 g.) (2,4,6-trinitro-derivative, m. p. and mixed m. p. 182—183°). (iii) A mixture, b. p. 76—80°/1 mm., 215°/761 mm., n_D^{23} 1·5339 (Found: Cl, 3·1; 3·3%), of 3-methyl- (2·53 g.) and 3-chloro-benzyl alcohol (0·37 g.), a portion of which (0·53 g.) gave isophthalic acid (0·53 g.), identified as previously. Another portion of the mixture, with 3,5-dinitrobenzoyl chloride at 100° (10 min.), yielded **3-*methylbenzyl* 3,5-*dinitrobenzoate***, needles (from ligroin), m. p. 108—109° (Found: N, 8·8. $C_{15}H_{12}O_6N_2$ requires N, 8·9%). (iv) A mixture, b. p. 80—83°/1 mm., 222°/761 mm., n_D^{23} 1·5383 (Found: Cl, 7·8, 7·9%), of 3-chloro- (1·0 g.) and 3-methyl-benzyl alcohol (2·15 g.). Oxidation of this (0·61 g.) produced *m*-chlorobenzoic (0·16 g.), m. p. and mixed m. p. 157—158°, and isophthalic acid (0·58 g.), separated by extraction with benzene, in which only the former acid is soluble. (v) Material, b. p. 84—86°/1 mm., 237°/760 mm., n_D^{23} 1·5447 (Found: Cl, 17·6, 17·7%), consisting of the same alcohols (1·80 and 0·72 g., respectively). Oxidation again gave a mixture of *m*-chlorobenzoic and isophthalic acid. Treatment with phenyl isocyanate and recrystallisation of the product gave the phenylurethane of 3-chlorobenzyl alcohol. (vi) Unchanged ether (6·13 g.). The chief products are thus 3-methyl- (5·40 g., 0·044 mole) and 3-chloro-benzyl alcohol (3·17 g., 0·022 mole).

4-*Chloro*-4'-*methoxydibenzyl Ether*.—Cleavage of this substance (30·0 g., 0·11 mole) gave the following: (i) Toluene (2·0 g.). (ii) *p*-Methoxytoluene, b. p. 62—66°/35 mm., 174—175°/760 mm., $n_D^{22·5}$ 1·5100 (5·68 g., 0·046 mole) (lit.,[6] b. p. 176°, n_D^{20} 1·512), oxidised by alkaline

[6] Huntress and Mulliken, "Identification of Pure Organic Compounds," 1946, Wiley and Sons, New York, p. 532.

XUM

potassium permanganate to *p*-anisic acid, m. p. and mixed m. p. 182—183°. (iii) 4-Chlorobenzyl alcohol, b. p. 92—97°/1 mm. (5·17 g., 0·036 mole), needles (from cyclohexane), m. p. 71—72°, undepressed by admixture with a sample prepared from 4-chlorobenzyl chloride by hydrolysis. (iv) Material, b. p. 160—164°/1 mm. (4·23 g.), which on addition of a few drops of ethanol deposited 4,4′-dimethoxybibenzyl (1·0 g., 0·004 mole), needles, m. p. 125—127° (Found: C, 79·5; H, 7·4. Calc. for $C_{16}H_{18}O_2$: C, 79·3; H, 7·4%). The supernatant liquid was mostly unchanged ether, b. p. 164°/1 mm., n_D^{22} 1·5695 (3·23 g., 0·012 mole). (v) An undistillable residue (2·6 g.). The principal products were thus toluene (0·022 mole), *p*-methoxytoluene (0·046 mole), 4-chlorobenzyl alcohol (0·036 mole) and 4,4′-dimethoxybibenzyl (0·004 mole).

3-Chloro-4′-methoxydibenzyl Ether.—The following fission products were obtained (from 30 g., 0·11 mole, of the ether): (i) 2,3-Dimethylbutane (0·3 g.); (ii) toluene (1·35 g., 0·015 mole); (iii) material, b. p. 92—94°/40 mm. (4·48 g.), n_D^{24} 1·5076 (further fractionated as described below), a sample of which (0·50 g.) gave *p*-anisic acid (0·47 g.); (iv) 3-chlorobenzyl alcohol, b. p. 76—78°/0·5 mm., 237°/763 mm. (1·43 g., 0·010 mole), $n_D^{24·5}$ 1·5445 (phenylurethane, m. p. and mixed m. p. 92—93°); (v) uncleaved ether (12·4 g., 0·047 mole); and (vi) a dark residue (4·8 g.) (bath up to 220°). Fraction (iii) above was redistilled, giving (*a*) material, b. p. 172—174°/760 mm. (0·70 g.), whose chlorine content (Found: Cl, 1·80%) showed it to be mostly *p*-methoxytoluene (0·65 g.), and (*b*) *p*-methoxytoluene, b. p. 175—176°/760 mm., n_D^{24} 1·5076 (3·7 g.) (lit., *m*-chlorotoluene, b. p. 162°; *p*-methoxytoluene, b. p. 175—176°). The main products isolated were thus *p*-methoxytoluene (0·036 mole) and 3-chlorobenzyl alcohol (0·010 mole). Ether cleaved was 0·067 mole.

4-Methyl-4′-phenyldibenzyl Ether.—The fission products from this ether (35 g., 0·12 mole) on distillation gave the following: (i) *p*-Xylene, b. p. 60°/75 mm. (2·3 g.), b. p. 138—140°/761 mm., n_D^{23} 1·4921, identified as previously. (ii) A mixture, b. p. 62—67°/0·1 mm. (7·65 g.), of 4-methylbenzyl alcohol and 4-methylbiphenyl whose oxygen content (Found: O, 9·15; 9·14%) showed it to consist of 5·33 g. of the former and 2·32 g. of the latter. It gave with phenyl isocyanate the phenylurethane of 4-methylbenzyl alcohol, m. p. and mixed m. p. 79—80°, and, on oxidation, 0·62 g. gave terephthalic (0·70 g.), and *p*-phenylbenzoic acid, m. p. 225—227° (0·09 g.) (lit., m. p. 228°) (Found: C, 78·6; H, 5·2. Calc. for $C_{13}H_{10}O_2$: C, 78·8; H, 5·05%). (iii) Material, b. p. 78—82°/0·1 mm. (5·8 g.) (Found: O, 1·89; 1·72%), consisting of 4-methylbenzyl alcohol (0·80 g.) and 4-methylbiphenyl (5·0 g.), a portion of which (0·61 g.) on oxidation yielded *p*-phenylbenzoic (0·48 g.) and terephthalic acid (0·23 g.). When recrystallised from methanol, the 4-methylbiphenyl had m. p. 48—48·5° (lit., m. p. 49—50°). (iv) 4-Phenylbenzyl alcohol, b. p. 120—126°/0·1 mm. (6·30 g.), which crystallised from benzene–cyclohexane in plates, m. p. and mixed m. p. 100—100·5° (α-naphthylurethane, m. p. and mixed m. p. 125—126°) (unchanged ether has b. p. ~178°/0·07 mm., m. p. 62—63°). (v). A residue (11·5 g.) which percolated in benzene–light petroleum (1 : 4) through alumina, giving unchanged ether, m. p. 62—63° (7·9 g.). The main cleavage products from the ether (27·1 g., 0·094 mole) were thus 4-methyl- (6·14 g., 0·050 mole) and 4-phenyl-benzyl alcohol (6·30 g., 0·034 mole).

Discussion

The cleavage mechanism proposed by Huang and Si-Hoe,[2] in which free alkyl radicals or hydrogen atoms are considered to be the reacting entities, has been confirmed by Norman and Waters,[7] who unambiguously demonstrated the existence of free radicals in the catalysed Grignard reaction and showed that such radicals dehydrogenated diethyl ether to the radical CHMe·EOt. More recently, the radical ·CHPh·O·CH_2Ph has been prepared from dibenzyl ether by the action of t-butoxy-radicals, and found to disproportionate to benzaldehyde and free benzyl.[8] If this mechanism is accepted, the fission of the dibenzyl ether R·C_6H_4·CH_2·O·CH_2·C_6H_4R′ to give a 50% or higher yield of the benzyl alcohol R·C_6H_4·CH_2·OH or of the toluene R′·C_6H_4Me would indicate that scission proceeds *via* the radical R·C_6H_4·$\dot{C}$H·O·CH_2·C_6H_4R′, and, since reaction takes the course involving the more stable radical-intermediate (steric factors being absent), it follows

[7] Norman and Waters, *J.*, 1957, 950.
[8] Huang and Si-Hoe, *Proc. Chem. Soc.*, 1957, 354; "Vistas in Free Radical Chemistry," W. A. Waters (editor), Pergamon Press, London, 1959, p. 242.

that, in stabilising power on the intermediate benzyl radical, R is superior to R', or *vice versa*.

Among the monosubstituted ethers (See Table 2, in which for completeness the results from Part III [2] have been included), 2-chlorodibenzyl ether gave inconclusive results, while the 2-methyl homologue was split in the same direction as the 4-isomer. Of greater significance is the finding that the 3-chloro-atom stabilises the benzyl radical more than hydrogen does. This leads to the conclusion that, except for the *ortho*-substituents in which steric effects might be of consequence, all the substituents studied, despite their divergent electronic effects, stabilise benzyl radicals with respect to hydrogen.

TABLE 2. *Cleavage of monosubstituted dibenzyl ethers*, $R{\cdot}C_6H_4{\cdot}CH_2{\cdot}O{\cdot}CH_2Ph$.

R	Cleavage (%)	Products	
		$R{\cdot}C_6H_4{\cdot}CH_2{\cdot}OH$ (%)	PhMe (%)
o-Me	100	54	37
m-Me	85	73	37
p-Me	98	71	48
p-Bu^t	100	75	32
p-Ph	88	71	—
o-Cl	83	46	37
m-Cl	100	52	35
,,	100	63 *	47
p-Cl	73	61	39
p-OMe	87	—	48

* Estimated by chlorine analyses of alcohol fractions (as for disubstituted ethers). Benzyl alcohol formed = 27%.

TABLE 3. *Cleavage of disubstituted dibenzyl ethers* $R{\cdot}C_6H_4{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}C_6H_4R'$.

	R	R'	Ether reacting (%)	Products		Inference (*re* stabilising influence)
				$R{\cdot}C_6H_4{\cdot}CH_2{\cdot}OH$ (%)	$R'{\cdot}C_6H_4{\cdot}CH_2{\cdot}OH$ (%)	
1	*p*-Me	*p*-Cl	76	47	43	*p*-Me ~ *p*-Cl
2	*p*-Me	*m*-Cl	69	68	25	*p*-Me > *m*-Cl
3	*p*-Me	*p*-Bu^t	80	1	79	*p*-Bu^t > *p*-Me
4	*p*-Me	*p*-Ph	78	54	36	*p*-Me > *p*-Ph
5	*m*-Me	*m*-Cl	76	57	29	*m*-Me > *m*-Cl
6	*p*-Cl	*p*-OMe	89	36	Traces *	*p*-Cl > *p*-OMe
7	*m*-Cl	*p*-OMe	59	15	Traces †	*m*-Cl ≥ *p*-OMe

* *p*-Methoxytoluene isolated in 55% yield. † *p*-Methoxytoluene isolated in 50% yield.

The results for the disubstituted ethers (see Table 3) allow a comparison to be made among the substituents themselves. The following scales of relative stabilising capacities can be set up: *p*-Bu^t > *p*-Me ~ *p*-Cl > *p*-OMe > H; *m*- and *p*-Me > *m*-Cl ≥ *p*-OMe > H; and *p*-Me > *p*-Ph > H. The high stabilising capacities of the alkyl groups are evident from all three scales, while the relation *m*-Cl ≥ *p*-OMe confirms the result from 3-chlorodibenzyl ether.

The uniformly greater stabilising influence, compared with hydrogen, of substituents of diverse electronic nature has been encountered in the substituted triphenylmethyls, which can be considered as substituted benzyl radicals, as measured by the degree of dissociation in solution of the corresponding hexa-arylethanes. This has been extensively investigated by Bowden and his co-workers [9] using the cryscopic technique, and by Marvel *et al.*,[10] who employ the magnetic susceptibility method. Unfortunately serious discrepancies exist

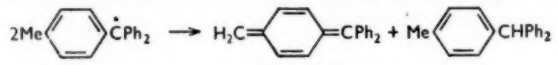
[9] (*a*) Bowden and Thomas, *J.*, 1940, 1242; Bowden and Clarke, *J.*, 1940, 883; (*b*) Bowden, *J.*, 1957, 4235; (*c*) Beynon and Bowden, *J.*, 1957, 4257; and other papers in the series.

[10] (*a*) Marvel, Riegel, and Mueller, *J. Amer. Chem. Soc.*, 1939, **61**, 2769; Marvel, Mueller, Himel, and Kaplan, *ibid.*, p. 2771; Marvel, Kaplan, and Himel, *ibid.*, 1941, **63**, 1892; (*b*) Marvel, Dietz, and Himel, *J. Org. Chem.*, 1942, **7**, 392; (*c*) Marvel, Whitson, and Johnston, *J. Amer. Chem. Soc.*, 1944, **66**, 415; (*d*) Marvel, Mueller, and Ginsberg, *ibid.*, 1939, **61**, 2008.

XUM

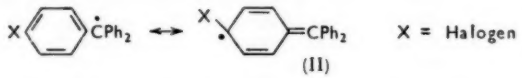
between results obtained by the two schools, although the validity of the magnetic method has recently been questioned.[9b,9c,11] Nevertheless, from both approaches the concordant conclusion emerges that, of the substituents studied, which included certain *m*- and *p*-alkyl, halogen, methoxy, and phenyl groups, all stabilise the resulting triphenylmethyl radical with respect to hydrogen.

Substituents whose effects could not satisfactorily be evaluated from dissociation of the hexa-arylethanes are the *p*-methyl group [9a,10a] and the *p*-halogen-atom.[9c,10b] With the former, the radical (I) is in part destroyed by intermolecular disproportionation:



(I)

while the latter is to some extent reduced by " molecular " silver, an effect attributed by Beynon and Bowden [9c] to the partially aliphatic character of the halogen atom due to participation by canonical structures such as (II). Side reactions of this nature (namely, intermolecular disproportionation or reduction [12] by the cobalt chloride–Grignard reagent) could occur with radicals derived from the dibenzyl ethers containing 4-methyl and 4-chloro-substituents, and would introduce moderate errors in the analysis of the cleavage products, especially where 4-chlorobenzyl alcohol is produced. However, that these side-reactions, if they took place, did so only to a small extent is evident from the following observations. (*a*) In the cleavage of 4-methyl- and 4-chloro-dibenzyl ether, good yields of the substituted benzyl alcohols were obtained. (*b*) With 3-chloro-4′-methyl- and 4-chloro-4′-methyl-dibenzyl ether, no less than 93 and 90%, respectively, of the ethers which reacted were accounted for as 4-methyl- and chloro-benzyl alcohol. (*c*) In the alcoholic fraction of the cleavage products of the last-named ether, a search for benzyl alcohol showed that none was present. It is concluded that the radicals formed from the dibenzyl ethers



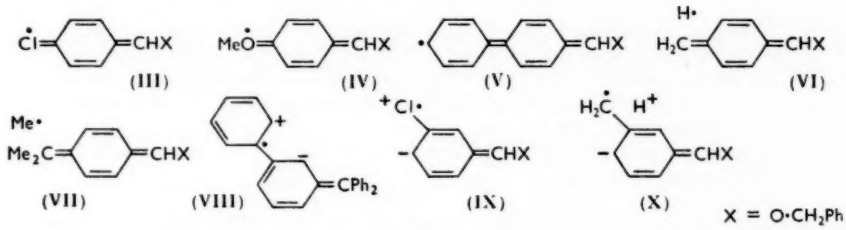
(II)

undergo intramolecular disproportionation into an aldehyde and a free benzyl radical relatively rapidly, before reduction by the Grignard reagent–cobaltous chloride mixture, or intermolecular disproportionation with a similar radical, can occur to any considerable extent. On the other hand, reduction of chlorine was quite appreciable in the 4-chlorobenzyl radicals, as shown, for instance, by the isolation of toluene from 4-chloro-4′-methyldibenzyl ether. This is not surprising considering the relatively long life of radicals of this type.

The greater stabilising capacity on benzyl radicals of all the substituents studied, compared with hydrogen, can be explained in terms of increased delocalisation of the unpaired electron by " homo-mesomerism " [13] due to the presence of the substituents. Thus, for the radicals obtained from 4-chloro-, 4-methoxy-, and 4-phenyl-dibenzyl ether, it would be expected that resonance hybrids such as (III), (IV), and (V), respectively, contribute to radical stability, while for the 4-methyl homologue, hyperconjugation would result in canonical structures such as (VI). For the 4-t-butyl group a hyperconjugative-like effect, analogous to that proposed by Brown *et al.*[14] in the solvolysis of αα-dimethylbenzyl chloride, could conceivably be invoked, resulting in resonance forms such as (VII) for the radical. However, the insufficiency of homo-mesomerism alone to account for

[11] Selwood and Dobres, *J. Amer. Chem. Soc.*, 1950, **72**, 3860.
[12] Cf. Huang, *J.*, 1954, 3084.
[13] See Remick, " Electronic Interpretations of Organic Chemistry," Chapman and Hall, London, 2nd edn., 1949, p. 62.
[14] Brown, Brady, Grayson, and Bonner, *J. Amer. Chem. Soc.*, 1957, **79**, 1897.

all the observed results is soon apparent. Thus the stabilising influence of the 3-methyl and the 3-chloro-substituent remains unexplained, while the contrasting electronic effects of such groups as 4-t-butyl and 3-chloro playing no part in determining radical-stability, seems difficult to understand. Moreover, the strikingly high stabilising power of the alkyl groups would have to be attributed entirely to hyperconjugation. This effect, if appreciable, is known to be small.



It appears clear that, in conjunction with the homo-mesomeric mechanism, polar effects must also operate in some measure to control radical-stability. For the *m*-phenyl group in the substituted triphenylmethyls,[10d] it has been suggested [15] that stabilisation is due to participation of dipolar-radicals such as (VIII). This could be envisaged for the radicals derived from 3-chloro- and 3-methyl-dibenzyl ether, resulting in contributions from radical-ions such as (IX) and (X). Thus the effects of the 3-chloro and the 3-methyl group could be rationalised in terms of a homo-mesomeric process dependent on the operation of a polar (mesomeric) mechanism. However, to explain the results for the substituents examined it appears to us that a more general effect, operating jointly with those above, has to be postulated, involving electronic interaction of the substituents with the radical centre (the α-carbon), relayed through both the inductive and the mesomeric mechanism. By this effect it is envisaged that electronegative substituents, such as 3- and 4-chloro, tend to withdraw the unpaired electron into the ring, thereby imparting to the radical some of the character of the benzylic cation, whereas with electron-repelling groups, such as 3- or 4-methyl or 4-t-butyl, the reverse occurs, the radical in this case acquiring the attributes of the benzylic anion. The resulting polar nature of the radical would then be expected to be conducive to radical-stabilisation (*a*) externally, by solvation with the solvent, and (*b*) internally, if the not unreasonable assumption is made that these resonance-stabilised ions are relatively more stable than the radical. The assumption that the benzyl cation is more stabilised than the corresponding radical finds experimental evidence from the electron impact measurements by Halpern,[16] who concludes that allyl and cumyl cations possess resonance energies an order of magnitude higher than the respective radicals, and derives theoretical support from the calculation by Muller and Mulliken [17] on the allyl ion and radical. That the benzyl anion is also relatively more stable than the radical, however, requires substantiation.

The authors are much indebted to Professor C. A. Coulson, F.R.S., and to Dr. W. A. Waters, F.R.S., for very helpful discussions.

UNIVERSITY OF MALAYA IN SINGAPORE,
SINGAPORE.

[*Received, February 6th,* 1959.]

[15] Lichtin and Glazer, *ibid.*, 1951, **73**, 5537.
[16] Halpern, *J. Chem. Phys.*, 1952, **20**, 744.
[17] Muller and Mulliken, *J. Amer. Chem. Soc.*, 1958, **80**, 3489.

XUM

648. *The Relative Stabilising Influences of Substituents on Free Alkyl Radicals. Part VII.*[1] *The Cleavage of Monosubstituted Dibenzyl Ethers by Free t-Butoxy-radicals.*

By R. L. Huang and Oon-Keong Yeo.

In the abstraction of α-hydrogens by t-butoxy-radicals from the ether $R{\cdot}C_6H_4{\cdot}CH_2{\cdot}O{\cdot}CH_2Ph$ the substituents R = 4-Bu^t, 4-OMe, and 4-Cl facilitate the reaction, while 3-Cl has little effect. The results are explained in terms of the stabilising influence of R on the benzyl radical produced, in conjunction with a polar effect.

Evidence for hydrogen-abstraction from the ether by the benzyl radicals $R{\cdot}C_6H_4{\cdot}CH_2{\cdot}$ is presented.

The cleavage of substituted dibenzyl ethers (I) by free alkyl radicals formed from Grignard reagents in the presence of cobaltous chloride has been studied in a

(I) $R{\cdot}C_6H_4{\cdot}CH_2{\cdot}O{\cdot}CH_2Ph$ $\qquad$ $R{\cdot}C_6H_4{\cdot}\dot{C}H{\cdot}O{\cdot}CH_2Ph$ (II)

comparison of the stabilising influences, relative to hydrogen, of the substituents R on free benzyl radicals.[1,2] The radical-intermediate (II) involved in the cleavage has since been shown in the case of dibenzyl ether to be generated also by free t-butoxy-radicals; its disproportionation products, benzaldehyde and free benzyl, being obtained, respectively, as the free aldehyde and substances derived from the radical.[3] Since aldehydes can readily be isolated, *e.g.*, *via* the bisulphite compounds, this reaction of t-butoxy-radicals provides a convenient method for studying the substituent effect on the cleavage of dibenzyl ethers. The fission by this method of five such ethers (I; R = 4-Me, -Bu^t, and -OMe, 3- and 4-Cl) is now reported.

Whereas in the catalysed Grignard reaction the aldehyde and free benzyl formed are efficiently reduced to the corresponding benzyl alcohol and toluene, which being immune to further reaction are obtained in good yield, with t-butoxy-radicals these disproportionation products react further to give a variety of substances.[3] Inasmuch as a 50% or higher yield of the main product is essential for a decision of the main direction of cleavage, it is important to ascertain the optimum conditions. Experiments conducted with this in view are summarised in the Table.

Among the secondary products (see Table), the substituted benzoic acids probably result mainly from oxidation of the aldehydes, while 3- and 4-chlorobenzyl alcohol, isolated in traces, probably arose by hydrolysis (during exhaustive extraction with aqueous sodium hydrogen sulphite) of the corresponding benzyl benzoate, derived from the radical (III), itself formed from the aldehyde as follows:

$$Ar{\cdot}CHO \xrightarrow{But O\cdot} Ar{\cdot}\dot{C}{:}O \xrightarrow{Ar{\cdot}CHO} Ar{\cdot}CO{\cdot}O{\cdot}\dot{C}HAr\ (III) \xrightarrow{Ether} Ar{\cdot}CO{\cdot}O{\cdot}CH_2Ar$$

Ar = *m*- and *p*-$Cl{\cdot}C_6H_4$–

The formation of the radical (III; Ar = Ph) from benzaldehyde and free t-butoxy-radicals is well known.[4] Of greater interest is the isolation, in yields of 12—24%, of the substituted toluene $R{\cdot}C_6H_4Me$ from most of the ethers. Formation of these toluenes probably occurs by hydrogen-abstraction by the free benzyl from the solvent ether, and strongly suggests

[1] Part VI, Huang and Singh, preceding paper.
[2] Huang and Si-Hoe, *J.*, 1957, 3988.
[3] Huang and Si-Hoe, *Proc. Chem. Soc.*, 1957, 354; "Vistas in Free Radical Chemistry," W. A. Waters (Editor), Pergamon Press, London, 1959, p. 242.
[4] Rust, Seubold, and Vaughan, *J. Amer. Chem. Soc.*, 1948, **70**, 3258.

that cleavage proceeds in part by a chain mechanism (though undoubtedly of a short chain-length) which for dibenzyl ether may be represented as follows:

$$Ph\cdot CH_2\cdot O\cdot CH_2Ph \xrightarrow{ButO\cdot} Ph\cdot\dot{C}H\cdot O\cdot CH_2Ph \quad (IV)$$

$$(IV) \longrightarrow Ph\cdot CHO + Ph\cdot CH_2\cdot$$

$$Ph\cdot CH_2\cdot + Ph\cdot CH_2\cdot O\cdot CH_2Ph \longrightarrow PhMe + (IV) \ldots \text{etc.}$$

Benzyl ethers thus appear to be susceptible to fission by radicals of a range of electronegativity, including substituted benzyl radicals, and free alkyl and alkyloxy-radicals.

Cleavage of monosubstituted dibenzyl ethers $R\cdot C_6H_4\cdot CH_2\cdot O\cdot CH_2Ph$ *by free t-butoxy-radicals.*

	Ether			Products $R\cdot C_6H_4\cdot CHO$ bisulphite compound (mmole) (%)
	R	Quantity used (mmole)	Quantity reacted (mmole)	Peroxide (mmole) (ratio, ether : peroxide)
1	*p*-Me	95	53	48 (2 : 1)	14 (26)
2	*p*-Bu^t	160	110	78 (2 : 1)	31 (28)
3	,,	79	36	20 (4 : 1)	16 (45)
4	,,	91	41	18 (5 : 1)	25 (61)
5	*p*-OMe	92	38	18 (5 : 1)	19 (50)
6	*m*-Cl	110	55	22 (5 : 1)	22 (40)
7	*p*-Cl	110	42	22 (5 : 1)	13 (31)
8	,,	130	71	65 (2 : 1)	29 (41)
9	,,	170	97	69 (2·5 : 1)	27 (28)
10	,,	170	35	86 (2 : 1) ¶	18 (51)

	Products				Yield of $R\cdot C_6H_4\cdot CHO$ + $R\cdot C_6H_4\cdot CO_2H$ (%)
	Ph·CHO bisulphite compound (mmole) (%)	$R\cdot C_6H_4\cdot CO_2H$ (mmole)	$R\cdot C_6H_4\cdot Me$ (mmole) (%)	Polymer (g.)	
1	7 (13)	0·2	—	6·3	26
2	4 (4)	0·7	14 (13) *	17·5	28
3	2 (5)	0·6	6·3 (19)	3·8	47
4	3 (8)	0·7	10 (24)	3·6	63
5	3 (8)	0·5	4·9 (13)	3·5	51
6	22 (40)	0·6	13 (24)	2·1 §	41
7	5 (12)	0·8	6·3 (15)	3·1	33
8	13 (18)	1·4	—	6·8 ‡	42
9	12 (12)	1·3	—	9·1 ‡ §	29
10	5 (14)	2·0	4·1 (12)	1·8 ¶	57

* Also isolated $[p\text{-}Bu^t\cdot C_6H_4\cdot CH_2]_2$ (3 mmoles). ‡ In open vessel under N_2. ¶ In open vessel at 110—115° for 38 hr., peroxide only partially decomposed. We thank Mr. Surinder Singh for collaboration in this experiment. § Traces of $R\cdot C_6H_4\cdot CH_2\cdot OH$ isolated.

Experimental

Cleavage Experiments.—A mixture of the ether and di-t-butyl peroxide was sealed under nitrogen in a glass tube, and heated at 110° for 96 hr. (experiments nos. 1—7). In some cases (nos. 8—10) the mixture was heated in an open flask under reflux, in an atmosphere of nitrogen. Optimum yields (nos. 4, 5, 6, and 10) were obtained by using a 5-fold excess of the ether, except for 4-chlorodibenzyl ether, for which a 2-fold excess for a shorter time (38 hr.) was preferable.

Analysis of Cleavage Products: Typical Procedures.—4-t-Butyldibenzyl ether. The reaction mixture from this ether (40·0 g., 160 mmoles) and t-butyl peroxide (11·4 g., 78 mmoles) was diluted with light petroleum (40 c.c.) and the homogeneous mixture was shaken with a saturated aqueous solution of sodium hydrogen sulphite (2 hr.). The bisulphite compounds (8·9 g.) were filtered off and washed with ether. The petroleum solution was further extracted with 10% aqueous sodium carbonate, dried ($MgSO_4$), concentrated, and distilled to give the following fractions: (i) *p*-t-Butyltoluene, b. p. 32—34°/0·5 mm., 191·5°/762 mm. (2·1 g.), n_D^{24} 1·4919

(lit.,[5] b. p. 192—193°/760 mm., n_D^{20} 1·4919) [dinitro-derivative, yellow plates (from ethanol), m. p. and mixed m. p. 96—97°, alone or mixed with an authentic sample]. (ii) Material, b. p. 144—158°/0·5 mm., n_D^{23} 1·5425 (12·5 g.) which deposited small quantities of *4,4'-di-t-butylbibenzyl* (0·61 g.) which crystallised from light petroleum in rhombic prisms, m. p. 150—151° (Found: C, 89·4; H, 10·2. $C_{22}H_{30}$ requires C, 89·8; H, 10·2%), the liquid being mostly unchanged ether (b. p. and *n*). (iii) A residue (17·8 g.), a portion (6·2 g.) of which was chromatographed in light petroleum on alumina, ten 30 c.c. fractions being collected. The first two of these gave traces (0·09 g.) of the above bibenzyl, and the later fractions intractable oils.

The sodium carbonate extract was washed with ether, and, after expulsion of dissolved ether by warming, was acidified with concentrated hydrochloric acid to give *p*-t-butylbenzoic acid, m. p. 159—163° (0·13 g.), raised to 163—164° by recrystallisation from light petroleum (Found: C, 74·4; H, 7·8. Calc. for $C_{11}H_{14}O_2$: C, 74·2; H, 7·9%). Marvel *et al.*[6] report m. p. 164°.

The mixture of aldehyde bisulphite compounds obtained as above was treated with 2N-sulphuric acid under nitrogen, and the aldehydes were liberated taken up in ether, washed with water, dried, and concentrated to a mixture (4·0 g.). A portion of this gave the *p*-t-butylbenzaldehyde *p*-nitrophenylhydrazone, yellow leaflets (from ethanol), m. p. 215—216° (Baker *et al.*[7] report m. p. 214°). Another portion (1·0 g.) was shaken with saturated aqueous alkaline potassium permanganate (*ca.* 20 c.c.) for 10 min., then heated with shaking at 60° for 30 min., cooled, and acidified with dilute sulphuric acid. After clarification with aqueous sodium hydrogen sulphite, the products were extracted with much ether, washed with water once, dried, and concentrated to give a solid, m. p. 158—165° (0·7 g.), which was mostly *p*-t-butylbenzoic acid. Fractional sublimation (at 110°/0·2 mm.) removed traces of benzoic acid (0·05 g.; m. p. and mixed m. p.), the *p*-t-butylbenzoic acid being then obtained as needles (from petroleum), m. p. and mixed m. p. 164—165° (0·65 g.). From the molar ratio of butylbenzoic and benzoic acid obtained, it is thus estimated that the mixture of bisulphite compounds obtained above (8·9 g.) is composed of approx. 31 and 4 mmoles of the bisulphite compounds of the respective aldehydes.

4-Chlorodibenzyl ether. This ether (25 g., 110 mmoles) and the peroxide (3·2 g., 22 mmoles) gave, as above, a mixture of bisulphite compounds, *p*-chlorobenzoic acid, m. p. and mixed m. p. 239—242° (0·13 g.), and a neutral fraction which was distilled to give (i) *p*-chlorotoluene, b. p. 42—50°/0·5 mm., 162°/760 mm. (0·8 g.), n_D^{23} 1·5187 (lit., b. p. 162°/760 mm., n_D^{19} 1·5199), (ii) unchanged ether (11·0 g.), and (iii) a residue (7·45 g.). The residue, on chromatography and distillation, gave more unchanged ether (4·4 g.). (In one experiment, traces of 4-chlorobenzyl alcohol were isolated; m. p. and mixed m. p. 70—71°.) The bisulphite compounds were decomposed as before, and the aldehyde mixture distilled *in vacuo*, a small forerun and residue being rejected (<10%). A chlorine analysis of the main distillate (Found: Cl, 19·0, 19·0%) enabled the molar ratio of chlorobenzaldehyde and benzaldehyde to be computed (subject probably to a maximum error of *ca.* 5%). A sample of the aldehyde mixture gave *p*-chlorobenzaldehyde 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 267—268° and an oxime, m. p. 109—110° (lit., m. p. 110°).

The cleavage products from 3-chlorodibenzyl ether were similarly worked up. The mixture of aldehydes from 4-methoxydibenzyl ether was estimated by methoxyl determinations.

Discussion

If the course of cleavage is governed soley by the relative stability of the radical intermediate, the results obtained (Table, nos. 4, 5, 6, and 10) show that, in their ability to stabilise benzyl radicals, the substituents 4-Bu^t, 4-OMe, and 4-Cl are all greater than, and 3-Cl is of the same order as, hydrogen. Recently, however, evidence has accumulated which indicates that in reactions involving radicals of relatively high electronegativity polar factors can also play an effective directing part, as for example in the abstraction of hydrogen, by chlorine atoms and by free benzoyloxy-radicals, from substituted toluenes,[8] aliphatic acids,[9] and aromatic aldehydes.[10] These effects appear significant only with

[5] Lacourt, *Bull. Soc. chim. belges*, 1929, **38**, 1.
[6] Marvel, Johnston, Meier, Mastin, Whitson, and Himel, *J. Amer. Chem. Soc.*, 1944, **66**, 914.
[7] Baker, Nathan, and Shoppee, *J.*, 1935, 1846.
[8] Helden and Kooyman, *Rec. Trav. chim.*, 1954, **73**, 269; Russell and Brown, *J. Amer. Chem. Soc.*, 1955, **77**, 4578; Russell, *ibid.*, 1956, **78**, 1047; Walling and Miller, *ibid.*, 1957, **79**, 4181.
[9] Price, *ibid.*, 1953, **75**, 3686.
[10] Walling and McElhill, *ibid.*, 1951, **73**, 2927.

highly electronegative radicals such as mentioned above (and presumably with electropositive ones also) but, as would be expected, not with relatively neutral radicals such as free alkyls,[9] or even trichloromethyl.[11] Since free t-butoxy is intermediate in electron-withdrawing character between the free alkyls and benzoyloxy, its reactions might similarly be influenced by polar effects. This has been found to be the case by Johnston and Williams,[12] who showed, contemporaneously with this work, that in the attack by this radical on substituted toluenes and cumenes the substituent assists or retards α-hydrogen-abstraction according to whether it is electron-repelling or -attracting. Such polar influence must to some extent operate also in the reaction with dibenzyl ethers. Thus the facilitating action of the 4-butyl and 4-methoxy-groups is attributed to two complementary effects: radical-stabilisation and electron-release. The 4-chloro-substituent represents a case of opposing influences: but, whereas in *p*-chlorotoluene the hindering polar factor seems overpowering (the rate of hydrogen-abstraction being 0·85 against 1 for toluene),[12] in the benzyl ether the reverse is the case, and this must be due to the presence of the electron-donating and resonance-stabilising benzyl ether grouping $-O\cdot CH_2Ph$. The same effect of this group has earlier been encountered by Russell [8] in the reaction of peroxy-radicals. The 3-chloro-atom is a similar combination of conflicting influences, and its indifferent directive capacity, compared with that of the 4-chloro-atom, can be explained in terms of a greater adverse polar effect coupled probably with decreased stabilisation. It is noteworthy that in the cleavage of 3-chlorodibenzyl ether by the cobalt chloride-catalysed Grignard reaction,[1] the radicals $3\text{-}Cl\cdot C_6H_4\cdot\dot{C}H\cdot O\cdot CH_2Ph$ and $3\text{-}Cl\cdot C_6H_4\cdot CH_2\cdot O\cdot\dot{C}HPh$ are formed in a molar ratio of **63 : 27**, whereas with t-butyl peroxide this ratio becomes **41 : 40**. In the former fission, relatively neutral alkyl radicals (or hydrogen atoms) react, and hence the stability factor predominates; in the latter, the unfavourable polar effect of the 3-chloro-substituent becomes significant, and the direction of cleavage is all but reversed. Again, with 4-chloro-4′-methoxydibenzyl ether, attacking alkyl radicals (from the catalysed Grignard reaction) rupture the ether largely via the radical-intermediate $4\text{-}Cl\cdot C_6H_4\cdot\dot{C}H\cdot O\cdot CH_2\cdot C_6H_4\cdot OMe\text{-}4$,[1] whereas free t-butoxy-radicals bring about fission equally in both directions, giving a mixture of *p*-chloro- and *p*-methoxybenzaldehyde in approximately the same molar proportions.[13] Here a favourable polar effect towards the electrophilic t-butoxy-radical is exerted by the 4-methoxy-group, probably augmented by the $-I$ effect of the 4-chlorine atom. It would be of interest to study cleavages by more strongly polar radicals, of both electropositive and electronegative character.

The authors thank Dr. W. A. Waters, F.R.S., for stimulating discussions.

UNIVERSITY OF MALAYA IN SINGAPORE,
SINGAPORE.

[*Received, February 6th*, 1959.]

[11] Kooyman, *Discuss. Faraday Soc.*, 1951, **10**, 163.
[12] Johnston and Williams, *Chem. and Ind.*, 1958, 328.
[13] Huang and Singh, unpublished result.

XUM

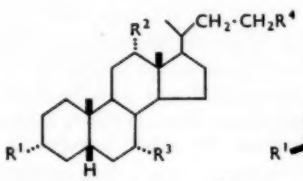
649. *The Steroid Series. Part IV.* Some Basic Derivatives.*

By A. F. Chaplin, D. H. Hey, and J. Honeyman.

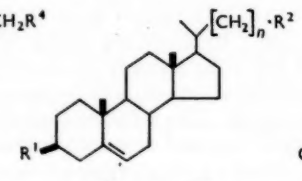
A number of amides of steroid acids has been prepared and converted into the corresponding amines by reduction. In this manner 24-aminocholan-3α-ol, 24-aminocholane-3α : 12α-diol, 24-aminocholane-3α : 7α : 12α-triol, 25-aminohomocholan-3α-ol, 22-aminobisnorchol-5-en-3β-ol, 23-aminonorchol-5-en-3β-ol and 24-aminochol-5-en-3β-ol were prepared. A preparation of 24-aminocholan-3-one is also described. A number of indolosteroids having the indole ring fused to ring A are described, and attempts to obtain indolosteroids having the indole ring fused to ring D are reported.

Interest in the biological activity of the steroidal alkaloids has stimulated the synthesis of simpler basic derivatives in this series by several groups of workers.[1] Gould and his co-workers [2] have reported that 3β-hydroxy-16α-piperidinopregn-5-en-20-one has the same kind of physiological properties as alkaloids of the veratrum group. The secondary amine 20-(5-methyl-2-piperidyl)pregn-5-ene-3β : 20-diol [3] has also been found to be active. Part of the present communication describes the preparation of steroids having a primary amino-group attached to the 17-side-chain.

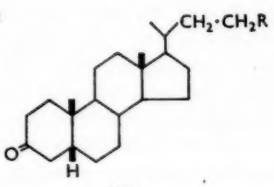
The acid chlorides of 3α-acetoxy-, 3α,12α-diformyloxy-, and 3α,7α,12α-triformyloxycholanic acid (I—III; $R^4 = CO_2H$), and 3β-acetoxybisnor- and 3β-acetoxy-chol-5-enic



	R^1	R^2	R^3
(I):	AcO	H	H
(II):	H·CO_2	H·CO_2	H
(III):	H·CO_2	H·CO_2	H·CO_2
(IV):	HO	H	H
(V):	HO	HO	H
(VI):	HO	HO	HO



	R^1	R^2
(VII):	AcO	CO_2H
(VIII):	AcO	COCl
(IX):	AcO	CO·NH_2
(X):	OH	NH_2



(XI)

acid (VII; $n = 0$ and 2, respectively), have been converted into the amides in high yield. The chloride (I; $R^4 = COCl$) was also converted into 3α-acetoxyhomocholanamide (I; $R^4 = CH_2{\cdot}CO{\cdot}NH_2$), and the chloride (VIII; $n = 0$) into 3β-acetoxynorchol-5-enamide (IX; $n = 1$) by the Arndt–Eistert reaction. Each amide was reduced by lithium aluminium hydride to the hydroxy-amine, the acetyl or formyl groups being removed at the same time. The seven free hydroxy-amines (IV—VI; $R^4 = CH_2{\cdot}NH_2$), (IV; $R^4 = CH_2{\cdot}CH_2{\cdot}NH_2$) and (X; $n = 1$, 2, and 3) were not isolated but were precipitated from ethereal solution as hydrochlorides. The three amines (X; $n = 1$, 2, and 3), which form members of a homologous series, have the 3β-hydroxyl group and the 5 : 6-double bond, which is present in many of the steroidal alkaloids. Three of the other amines have the same side-chain attached to position 17 as the amine (X; $n = 3$) but show variations in other parts of the molecule. Thus they all have the 3α-hydroxy-A/B-*cis* ring fusion typical

* Part III, *J.*, 1954, 185.

[1] Barnett, Ryman, and Smith, *J.*, 1946, 524, 526, 528; James, Smith, Stacey, and Webb, *ibid.*, p. 665; Jones, Webb, and Smith, *J.*, 1949, 2164; Fieser and Huang, *J. Amer. Chem. Soc.*, 1953, **75**, 6306; Louw, Strating, and Backer, *Rec. Trav. chim.*, 1954, **73**, 667; 1955, **74**, 1540; Micheli and Bradsher, *J. Amer. Chem. Soc.*, 1955, **77**, 4788; Herzog, Payne, and Hershberg, *ibid.*, 1955, **77**, 5324, etc.

[2] Gould, Shapiro, and Hershberg, *J. Amer. Chem. Soc.*, 1954, **76**, 5567; Gould, Shapiro, Finckenor, Gruen, and Hershberg, *ibid.*, 1956, **78**, 3158.

[3] Uhle, *ibid.*, 1951, **73**, 883.

of the bile acids, whilst the amines (V and VI; $R^4 = CH_2{\cdot}NH_2$) have the 12α-hydroxyl group as in the steroidal alkaloid rubijervine. A homologue of the amine (IV; $R^4 = CH_2{\cdot}NH_2$) is also reported.

In order to obtain a keto-steroid having a basic group in the 17-side-chain, 3α-acetoxycholanamide (I; $R^4 = CO{\cdot}NH_2$) was converted into 3α-hydroxycholanamide (IV; $R^4 = CO{\cdot}NH_2$), which was oxidised to 3-oxocholanamide (XI; $R = CO{\cdot}NH_2$). The method of Heyl and Herr [4] was used for the protection of the keto-group. The pyrrolidyl derivative from the amide (XI; $R = CO{\cdot}NH_2$) was reduced to the amine, which was converted into 24-aminocholan-3-one hydrochloride (XI; $R = CH_2{\cdot}NH_2,HCl$). The infrared spectrum of this salt has a peak at 1719 cm.$^{-1}$, which is consistent with a keto-steroid structure.[5] An amorphous product is deposited from an aqueous-ethanolic solution of this salt if it is boiled or kept for a few hours at room temperature. Such amorphous products, which are considered to arise from the condensation of the keto-group of one molecule with the amino-group of another, have been reported by other workers.[6]

A second approach to the synthesis of basic derivatives in the steroid series involved the preparation of indolo-steroids in which the nitrogen-containing ring of indole is fused to ring A of the steroid molecule. By employing the combination of an indole system with a second basic group in the 17-side-chain, it was hoped that salts soluble in water would be obtained. Antaki and Petrow [7] had attempted to prepare such a compound from methyl 3-oxo*allo*cholanate by the Curtius reaction on the carboxyl group of indolo(3′ : 2′-2 : 3)-*allo*chol-2-enic acid, but could only obtain the required intermediate hydrazide in very low yield.

It is now shown that when methyl 3-oxocholanate (XI; $R = CO_2Me$) is heated with phenylhydrazine in glacial acetic acid an indolo-steroid is obtained. This conclusion is supported by the elementary analysis and the infrared spectrum. Although a linear or an angular formulation, corresponding to ring-closure on to position 2 or 4 respectively, is possible for this compound, Antaki and Petrow [7] have concluded that indolo-steroids derived from 3-keto-steroids of the normal series have the angular formulation. The reactivity of the 4-methylene group of 3-keto-steroids in the normal series is well known, and it is reasonable to suppose that ring closure of the keto-steroid phenylhydrazone on to the 4-position will occur. Thus the indolo-steroid prepared from methyl 3-oxocholanate is tentatively assigned the angular structure methyl indolo(2′ : 3′-3 : 4)chol-3-enate (XII; $R^1 = CO_2Me$, $R^2 = R^3 = H$). This ester was hydrolysed to the acid (XII; $R^1 = CO_2H$, $R^2 = R^3 = H$), but attempts to convert the carboxyl group into the amide gave a product which could not be obtained pure. The infrared spectrum of the crude product has, however, two broad bands (one is of high intensity; the other, medium) in the 1600—1700 cm.$^{-1}$ region, indicating that a primary amide group may be present. In another attempt to prepare this amide, 3-oxocholanamide was heated with phenylhydrazine in acetic acid solution. Again the product could not be crystallised. Its infrared spectrum, with a very strong peak near 750 cm.$^{-1}$ and no peaks near 700 cm.$^{-1}$, indicates the absence of a monosubstituted benzene ring and hence the product may be the indolo-steroidal amide (XII; $R^1 = CO{\cdot}NH_2$, $R^2 = R^3 = H$). As the amide could not be obtained pure the crude product in ether was reduced with lithium aluminium hydride. After reaction dry hydrogen chloride was passed into an ethereal extract of the product, which precipitated 24-aminoindolo-(2′ : 3′-3 : 4)chol-3-ene hydrochloride (XII; $R^1 = CH_2{\cdot}NH_2,HCl$; $R^2 = R^3 = H$). The same salt was also prepared from 24-aminocholan-3-one hydrochloride by reaction with phenylhydrazine in boiling methanol containing hydrochloric acid. The two methods of preparation of this salt gave products having identical infrared spectra.

In an attempt to obtain an indolo-steroid with greater solubility in water the synthesis

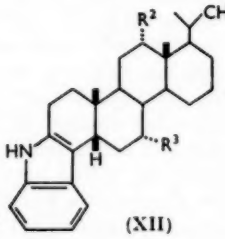
[4] Heyl and Herr, *J. Amer. Chem. Soc.*, 1953, **75**, 1918.
[5] Jones, Humphries, and Dobriner, *ibid.*, 1950, **72**, 956.
[6] Julian, Meyer, Cole, and Magnani, U.S.P. 2,566,336.
[7] Antaki and Petrov *J.*, 1951, 901.

XUM

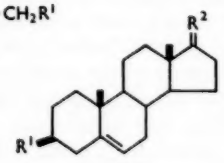
of an indolo-steroid containing two hydroxyl groups was undertaken. Methyl cholate was partially oxidised by the Oppenauer procedure to methyl 7α : 12α-dihydroxy-3-oxocholanate by following Pietra and Traverso's method.[8] Reaction of this compound with phenylhydrazine in acetic acid gave a product which did not crystallise, but, when the diacetylated ester was subjected to the Fischer indole synthesis, methyl 7α : 12α-diacetoxyindolo(2′ : 3′-3 : 4)chol-3-enate (XII; $R^1 = CO_2Me$, $R^2 = R^3 = OAc$) was readily obtained, which was hydrolysed to 7α : 12α-dihydroxyindolo(2′ : 3′-3 : 4)chol-3-enic acid (XII; $R^1 = CO_2H$, $R^2 = R^3 = OH$) in excellent yield. This acid was more soluble in water than indolo(2′ : 3′-3 : 4)chol-3-enic acid.

In order to confirm that no reaction other than hydrolysis of the ester groups of the indolo-steroid (XII; $R^1 = CO_2Me$, $R^2 = R^3 = OAc$) had occurred in the final stage of the above preparation an attempt was made to reconvert the dihydroxy-acid into methyl 7α : 12α-diacetoxyindolo(2′ : 3′-3 : 4)chol-3-enate. The dihydroxy-acid was acetylated by Whitman and Schwenk's method,[9] and the resulting product, after treatment with diazomethane, proved to be methyl 7α : 12α-diacetoxy-*N*-acetylindolo(2′ : 3′-3 : 4)chol-3-enate, identical with the product obtained by acetylation of methyl 7α : 12α-diacetoxyindolo-(2′ : 3′-3 : 4)chol-3-enate (XII; $R^1 = CO_2Me$, $R^2 = R^3 = OAc$).

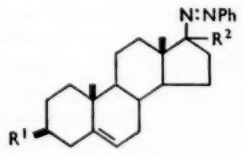
In an attempt to obtain a steroid with a nitrogen-containing heterocyclic ring fused to positions 16 and 17 of ring D, a structure which is common in steroidal alkaloids, dehydro-*epi*androsterone was heated with phenylhydrazine in acetic acid. The product, which crystallised from benzene–light petroleum in *yellow* needles, m. p. 151—151·5° (decomp.), was neither an indolo-steroid nor the phenylhydrazone. Oxidation of the phenylhydrazone is presumed to have taken place to give the hydroperoxide (XIV; $R^1 = OH$, $R^2 = O{\cdot}OH$). Similar reactions have been previously reported by Pausacker.[10] When dehydro*epi*-androsterone was heated with phenylhydrazine in ethanol containing a few drops of concentrated hydrochloric acid, the cooled solution deposited *colourless* needles which, on recrystallisation from benzene, became tinged with yellow. Analysis indicated that they could consist of a mixture of the phenylhydrazone (XIII; $R^1 = OH$, $R^2 = N{\cdot}NHPh$) and the hydroperoxide (XIV; $R^1 = OH$, $R^2 = O{\cdot}OH$). Repeated recrystallisation from ethanol gave the pure hydroperoxide. When, however, dehydro*epi*androsterone acetate was caused to react with phenylhydrazine in ethanol containing hydrochloric acid, *colourless*



(XII)



(XIII)



(XIV)

needles, m. p. 177—178°, separated from the reaction mixture. Rapid recrystallisation of this product from ethanol gave colourless needles, m. p. 137—142°, which gave correct analyses for dehydro*epi*androsterone acetate phenylhydrazone (XIII; $R^1 = OAc$, $R^2 = N{\cdot}NHPh$). The infrared spectra of the products of m. p. 177—178° and m. p. 137—142° are identical. Repeated recrystallisation of the phenylhydrazone (XIII; $R^1 = OAc$, $R^2 = N{\cdot}NHPh$) from benzene–light petroleum gave yellow leaflets, m. p. 154·5—155° (decomp.), identical with the hydroperoxide (XIV; $R^1 = OAc$, $R^2 = O{\cdot}OH$) obtained from the oxidation of the phenylhydrazone of dehydro*epi*androsterone acetate. Reduction of the hydroperoxide in ether with lithium aluminium hydride and crystallisation of the product

[8] Pietra and Traverso, *Gazzetta*, 1951, **81**, 687.
[9] Whitman and Schwenk, *J. Amer. Chem. Soc.*, 1946, **68**, 1865.
[10] Pausacker, *J.*, 1950, 3478.

from dilute ethanol gave 17ξ-phenylazoandrost-5-en-3β-ol (XIV; $R^1 = OH$, $R^2 = H$) in *yellow* needles, m. p. 214—216°. As reduction of a hydroperoxide with lithium aluminium hydride generally gives the corresponding hydroxy-compound, the formation of this product is difficult to interpret. Acetylation of the azo-compound (XIV; $R^1 = OH$, $R^2 = H$), m. p. 214—216°, with acetic anhydride in pyridine gave yellow needles of the acetate (XIV; $R^1 = OAc$, $R^2 = H$), m. p. 173—174°, depressed on admixture with the isomeric phenylhydrazone (XIII; $R^1 = OAc$, $R^2 = N{\cdot}NHPh$). In the presence of mineral acid mixed azo-compounds readily change into the isomeric hydrazone. Thus acetylation of the *yellow* azo-compound (XIV; $R^1 = OH$, $R^2 = H$), m. p. 214—216°, by Whitman and Schwenk's method [9] gave *colourless* needles, m. p. 137—142°, of dehydro*epi*androsterone acetate phenylhydrazone. A solution of the yellow azo-steroid (XIV; $R^1 = OH$, $R^2 = H$) in ethanol became colourless when acidified. From this mixture, after it had been heated for one hour and then kept overnight, dehydro*epi*androsterone was isolated. Presumably the azo-steroid (XIV; $R^1 = OH$, $R^2 = H$), when acidified, changes rapidly into the more stable phenylhydrazone (XIII; $R^1 = OH$, $R^2 = N{\cdot}NHPh$), which is then hydrolysed to the keto-steroid (XIII; $R^1 = OH$, $R^2 = O$).

Dehydro*epi*androsterone acetate phenylhydrazone was recovered unchanged after being heated in boiling acetic acid for 18 hours or shaken at room temperature with hydrochloric acid; when it was heated in a boiling solution of hydrochloric acid, it was hydrolysed to dehydro*epi*androsterone.

Experimental

Unless otherwise stated, the light petroleum has b. p. 60—80°. Solutions were dried, when appropriate, over anhydrous sodium sulphate before being evaporated under reduced pressure. The chromatography column, of internal diameter 2 cm., was packed with " neutral " alumina, type H, 200/250 mesh, supplied by P. Spence and Sons Ltd., Widnes. When required dry, benzene and ether were kept over sodium wire; chloroform was kept over calcium chloride. Ultraviolet absorption spectra were determined with a Unicam S.P. 500 spectrophotometer. Infrared absorption spectra were of Nujol mulls in a Grubb-Parsons double-beam S3 instrument. In all determinations of $[\alpha]_D$ the temperature was about 20° and *c* about 1.

Preparation of the Amides.—3α-Acetoxycholanic acid [11] (3·8 g.), 3α : 12α-diformyloxycholanic acid [12] (4 g.), 3α : 7α : 12α-triformyloxycholanic acid [12] (5 g.), 3β-acetoxybisnorchol-5-enic acid [13] (3 g.), and 3β-acetoxychol-5-enic acid [14] (1 g.) were converted into the corresponding amides by the method described below.

Redistilled thionyl chloride (2 ml. per g. of acid) and pyridine (0·1 ml.) were added to the acid in dry benzene (10 ml. per g. of acid). The mixture was left at room temperature for 4 hr., moisture being excluded. The solution was evaporated below 30°. More benzene was then added, and removed similarly. Excess of gaseous ammonia was passed into a cooled solution of the freshly prepared acid chloride in dry benzene, and the mixture was kept overnight at room temperature. The mixture was then diluted with methylene chloride and washed successively with water, dilute sulphuric acid, 3% aqueous sodium carbonate, and with water. Evaporation of the solution yielded the crude amide. In this manner, 3α-acetoxycholanamide (90%), m. p. 193—196° (Ercoli and De Ruggieri [15] recorded m. p. 193°), 3α : 12α-diformyloxycholanamide (93%), gum, 3α : 7α : 12α-triformyloxycholanamide (98%), m. p. 183—187° (Cortese and Bauman [16] recorded m. p. 187°), 3β-acetoxybisnorchol-5-enamide (90%), m. p. 223—225° (Cole and Julian [17] recorded m. p. 227—229°), and 3β-acetoxychol-5-enamide (95%), m. p. 215—218°, were prepared and were used without further purification. Crystallisation of 3β-*acetoxychol-5-enamide* from dilute ethanol gave plates, m. p. 217—218° (Found: C, 75·0; H, 10·05. $C_{26}H_{41}O_3N$ requires C, 75·1; H, 9·9%).

3α-*Acetoxyhomocholanamide.*—Redistilled thionyl chloride (5 ml.) and pyridine (1 drop) were

[11] Reindel and Niederländer, *Ber.*, 1935, **68**, 1969.
[12] Hughes, Smith, and Webb, *J.*, 1949, 3437.
[13] Smith and Wallis, *J. Org. Chem.*, 1954, **19**, 1628.
[14] Ruzicka and Wettstein, *Helv. Chim. Acta*, 1935, **18**, 986.
[15] Ercoli and De Ruggieri, *Farm. Sci. e tec* (*Pavia*), 1951, **6**, 547.
[16] Cortese and Bauman, *J. Amer. Chem. Soc.*, 1935, **57**, 1393.
[17] Cole and Julian, *ibid.*, 1945, **67**, 1369.

XUM

added to 3α-acetoxycholanic acid (3·7 g.) in dry benzene (50 ml.), and the mixture was left at room temperature for 4 hr. with the exclusion of moisture. The solution was evaporated below 30°. More benzene was then added and removed similarly, yielding the crude acid chloride, which was suspended in dry ether (50 ml.) and stirred into a solution at 0° of diazomethane (*ca.* 7 g.) in ether (200 ml.). After being stirred at 0° for 3 hr. the mixture was left at room temperature overnight. Evaporation below 30° of the filtered solution yielded the crude diazo-ketone, m. p. 127·5—128·5° (decomp.), which was immediately dissolved in dioxan (30 ml.) and then stirred into dioxan (90 ml.) and water (2 ml.) saturated with gaseous ammonia. Ammoniacal silver nitrate (10 ml.) was added dropwise to the vigorously stirred solution, which was slowly heated to 60° and maintained at that temperature for 2 hr. The mixture was then heated to 80° for ½ hr., cooled, and centrifuged. The mother-liquor, diluted with methylene chloride, was washed successively with 2N-nitric acid (200 ml.), 5% aqueous sodium carbonate (200 ml.), and water (200 ml.). Evaporation of the dry solution yielded a brown solid which, in benzene (20 ml.), was chromatographed on alumina (20 g.). Elution with benzene (150 ml.) gave a gum, which crystallised from light petroleum (b. p. 100—120°) in needles (0·55 g.), m. p. 162—164°. Further elution with benzene (1800 ml.), followed by benzene–ether (9 : 1; 300 ml.), gave a solid (1·3 g.), m. p. 163—166°, and ether–benzene (1 : 1; 200 ml.) afforded a solid (0·29 g.), m. p. 160—163°. Finally, elution with ether (500 ml.) and with ethanol (500 ml.) produced a gum, which did not crystallise. The solid isolated from the chromatogram crystallised from light petroleum (b. p. 100—120°) to give 3α-*acetoxyhomocholanamide* (1·8 g.) in needles, m. p. 166·5—167·5°, $[\alpha]_D$ +47° (in chloroform) (Found, after drying at 80°/15 cm. for 3 hr.: C, 75·2; H, 10·4. $C_{27}H_{45}O_3N$ requires C, 75·1; H, 10·5%).

3β-*Acetoxynorchol-5-enamide*.—A suspension in dry ether (50 ml.) of the crude acid chloride, prepared from 3β-acetoxybisnorchol-5-enic acid (2 g.) and thionyl chloride (5 ml.) as described in the experiment above, was added to cooled ethereal diazomethane (*ca.* 5 g. in 200 ml.). The mixture was left for 3 hr. at −10° and 14 hr. at room temperature and then filtered. Evaporation of the filtrate gave a pale yellow solid, which was added to dioxan (150 ml.) and water (2 ml.) saturated with gaseous ammonia. The stirred mixture at 60° was treated with ammoniacal silver nitrate (10 ml.) for 2 hr., and then the product was isolated as in the previous experiment. Elution from alumina (20 g.) with benzene (800 ml.) yielded no solid. Benzene–ether (4 : 1, 300 ml.; 1 : 1, 100 ml.) removed a gum (0·165 g.) which crystallised from a mixture of methylene chloride, light petroleum, and benzene in prisms (0·08 g.), m. p. 278—280° (decomp.). Elution with ether (300 ml.) and ether–ethanol (9 : 1, 200 ml.; 7 : 3, 1250 ml.) gave crystals (0·66 g.), m. p. 279—282° (decomp.). Final elution of the column with chloroform (300 ml.) and with ethanol (500 ml.) gave no crystalline products. The amide (36%), m. p. 278—282° (decomp.), recrystallised from methylene chloride–light petroleum–benzene in stocky prisms, m. p. 281—283° (decomp.). Herr and Heyl [18] prepared this amide, m. p. 283—285° (decomp.), by a different method.

3α-*Hydroxycholanamide* (*Lithocholamide*).—3α-Acetoxycholanamide (4 g.), m. p. 193—196°, was hydrolysed with boiling methanolic potassium hydroxide (5%; 80 ml.) to give 3α-hydroxycholanamide (3·4 g.) in needles (from methanol), m. p. 214·5—216·5°, $[\alpha]_D$ +35° (in ethanol). Louw *et al.*[19] recorded m. p. 211·5—213·5°.

3-*Oxocholanamide*.—Sodium chromate (1 g.) in acetic acid (20 ml.) was added to a solution of 3α-hydroxycholanamide (2 g.) in glacial acetic acid (40 ml.). The mixture was kept at 35° ± 1° for 6 hr., and then stirred into iced water (500 ml.). The precipitate was filtered off, washed with water, and dried. Crystallisation from aqueous ethanol gave leaflets (1·6 g.) of 3-*oxocholanamide*, m. p. 191—192°, $[\alpha]_D$ +34° (in chloroform) (Found: C, 73·4; H, 10·2. $C_{24}H_{39}O_2N,H_2O$ requires C, 73·6; H, 10·5%).

Preparation of the Amine Hydrochlorides.—The amides described above were reduced to the amines and isolated as hydrochlorides by the following method: The amide, in a Soxhlet extractor, was extracted with ether into lithium aluminium hydride (2—3 mol. excess) in boiling ether (450 ml.). The base was isolated in the normal manner in ethereal solution into which dry hydrogen chloride was passed until precipitation was complete. The crude amine hydrochloride was collected, washed with ether, and dried in a vacuum-desiccator over phosphorus pentoxide. In this manner, 3β-acetoxybisnorchol-5-enamide (0·2 g.) was converted into 22-*aminobisnorchol-5-en*-3β-*ol hydrochloride* (76%), which crystallised from ethanol–ether

[18] Herr and Heyl, *J. Amer. Chem. Soc.*, 1950, **72**, 1753.
[19] Louw, Strating, and Backer, *Rec. Trav. chim.*, 1954, **73**, 671.

in needles (Found: C, 71·6; H, 10·2. $C_{22}H_{37}ON,HCl$ requires C, 71·8; H, 10·3%). The hydrochloride decomposes when heated, but does not melt below 300°. 3β-Acetoxynorchol-5-enamide (0·2 g.), subjected to the same sequence of reactions, gave *23-aminonorchol-5-en-3β-ol hydrochloride* (49%), which crystallised from ethanol–ether in needles, m. p. *ca.* 300° (decomp.) (Found: C, 69·2; H, 10·1. $C_{23}H_{39}ON,HCl,H_2O$ requires C, 69·3; H, 10·5%).

In similar manner 3β-acetoxychol-5-enamide (0·4 g.) gave *24-aminochol-5-en-3β-ol hydrochloride* (75%), which crystallised from aqueous ethanol in needles, m. p. *ca.* 300° (decomp.) (Found: C, 70·1; H, 10·8; N, 3·55. $C_{24}H_{41}ON,HCl,H_2O$ requires C, 69·65; H, 10·7; N, 3·4%). 3α-Acetoxycholanamide (1·5 g.) gave the crude hydrochloride (73%), crystallisation of which from ether–ethanol afforded 24-aminocholan-3α-ol hydrochloride in needles, m. p. *ca.* 300° (decomp.), $[\alpha]_D$ +33·7° (in ethanol). Wesseley and Swoboda [20] reported m. p. *ca.* 300° with sintering at 260°, $[\alpha]_D$ +32·4° (in ethanol). 3α : 12α-Diformyloxycholanamide (1·7 g.) gave 24-aminocholane-3α : 12α-diol hydrochloride (61%) in prisms, m. p. 275—277° (decomp.), $[\alpha]_D$ +52·7° (in ethanol). Wesseley and Swoboda [20] recorded m. p. 276—278°, $[\alpha]_D$ +53·2° (in ethanol). 24-Aminocholane-3α : 7α : 12α-triol hydrochloride, formed from 3α : 7α : 12α-triformyloxycholanamide (0·4 g.), separated from ether–ethanol in needles (64%), m. p. 270° (decomp.), $[\alpha]_D$ +33° (in ethanol). Wesseley and Swoboda [20] recorded m. p. 270—271°, $[\alpha]_D$ +33·1° (in ethanol). Similarly, 3α-acetoxyhomocholanamide (0·22 g.) gave *25-aminohomocholan-3α-ol hydrochloride* (58%), which decomposed above 250°. Crystallisation from ether–ethanol afforded prisms (Found: C, 72·4; H, 11·3. $C_{25}H_{45}ON,HCl$ requires C, 72·9; H, 11·2%).

24-Aminocholan-3-one Hydrochloride.—3-Oxocholanamide (0·5 g.), m. p. 189·5—191°, in " AnalaR " benzene (50 ml.), was boiled under reflux until no more moisture was deposited in a Dean and Stark moisture trap. The solution was cooled and pyrrolidine (0·6 g.) was added (cf. ref. 4). The mixture was then vigorously stirred and boiled under reflux overnight; water was collected in the trap. Removal of the solvents, by distillation under reduced pressure, left a gum which solidified on trituration with ether. The crude enamine was separated from the ether, immediately placed in a sintered-glass crucible inside a Soxhlet extractor, and reduced with lithium aluminium hydride (1 g.) in boiling ether (250 ml.). When all of the amide had dissolved, the reduction was continued for a further 8 hr., after which the mixture was cooled and water (3 ml.) was added cautiously. After the contents of the flask had been boiled under reflux for 0·5 hr. and filtered, the ethereal layer was collected. The precipitate was twice extracted with more boiling ether in a similar manner. Dry hydrogen chloride was passed into the combined and dried (Na_2SO_4) ethereal solution until precipitation was complete. The crude amine hydrochloride was filtered off, washed with ether, and dried. Crystallisation from aqueous ethanol furnished *24-aminocholan-3-one hydrochloride* (57%) in needles which began to char at about 200°, but did not melt below 300° (Found: Cl, 9·2. $C_{24}H_{41}ON,HCl$ requires Cl, 9·0%). The infrared spectrum of this compound has a prominent peak at 1719 $cm.^{-1}$. When a solution of the salt in aqueous ethanol was left at room temperature, or boiled for a few minutes, an amorphous solid was precipitated.

Methyl Indolo(2′ : 3′-3 : 4)chol-3-enate.—Methyl 3-oxocholanate [21] (1·5 g.) and phenylhydrazine (15 g.) were heated with glacial acetic acid (50 ml.) on a steam-bath for 1 hr. The mixture was then stirred into iced water (300 ml.) containing hydrochloric acid (*d* 1·18; 5 ml.). The precipitated pale yellow solid (1·6 g.) crystallised from ethanol, to give needles (1·2 g.) of *methyl indolo*(2′ : 3′-3 : 4)chol-3-enate, m. p. 158—160°, $[\alpha]_D$ +152° (in chloroform) (Found: C, 80·6; H, 9·3; N, 2·7. $C_{31}H_{43}O_2N$ requires C, 80·7; H, 9·4; N, 3·0%). The infrared absorption spectrum has a strong band at 746 $cm.^{-1}$, but no bands near 700 $cm.^{-1}$.

Indolo(2′ : 3′-3 : 4)chol-3-enic Acid.—Methyl indolo(2′ : 3′-3 : 4)chol-3-enate (0·3 g.) and potassium hydroxide (14 g.) in 1 : 1 aqueous methanol (70 ml.) were boiled under reflux for 4 hr. The solution was diluted with water, concentrated under reduced pressure, and acidified with dilute hydrochloric acid. Crystallisation of the resulting precipitate from aqueous ethanol gave a pale yellow powder (0·22 g.), m. p. 184—186°. Repeated recrystallisations from the same solvent gave stocky needles of *indolo*(2′ : 3′-3 : 4)*chol-3-enic acid*, m. p. 209° with softening below 200° (Found: C, 76·7; H, 9·2; N, 3·1. $C_{30}H_{41}O_2N,H_2O$ requires C, 77·4; H, 9·3; N, 3·0%).

Indolo(2′ : 3′-3 : 4)chol-3-enamide.—(i) Thionyl chloride (5 ml.) and pyridine (1 drop) were added to indolo(2′ : 3′-3 : 4)chol-3-enic acid (0·3 g.) in dry ether (30 ml.), and the mixture kept

[20] Wesseley and Swoboda, *Monatsh.*, 1951, **82**, 437.
[21] Fieser and Ettorre, *J. Amer. Chem. Soc.*, 1953, **75**, 1700.

at room temperature for 4 hr. The solvent was removed below 30° and benzene was then added to the residue and removed similarly. The resultant gum was stirred with ammonia solution (*d* 0·88; 50 ml.) for 1 hr. and the mixture was then filtered. Attempts to crystallise the precipitate of crude amide, m. p. 130—150°, were unsuccessful. It could not be purified by chromatography. The infrared absorption spectrum of the compound has two prominent peaks in the 1600—1700 cm.$^{-1}$ range, a peak near 750 cm.$^{-1}$, but no peak near 700 cm.$^{-1}$.

(ii) 3-Oxocholanamide (0·2 g.) and phenylhydrazine (0·2 g.) were heated with glacial acetic acid (30 ml.) on a steam-bath for 1 hr., and then the mixture was stirred into iced 0·2N-hydrochloric acid (150 ml.). The precipitated solid (0·24 g.) was collected, but it did not crystallise. The infrared spectrum has prominent peaks in the same positions as those of the spectrum of the amide prepared by method (i).

24-Aminoindolo(2′ : 3′-3 : 4)chol-3-ene Hydrochloride.—(i) The crude amide of indolo(2′ : 3′-3 : 4)chol-3-enic acid (0·2 g.), in dioxan (20 ml.), was added dropwise to a boiling solution of lithium aluminium hydride (0·5 g.) in dioxan (150 ml.). The mixture was boiled under reflux for 12 hr., then cooled, and water (2 ml.) was cautiously added. When effervescence had ceased, the mixture was boiled under reflux for 30 min. and cooled. The precipitate was filtered off and extracted several times with boiling ether. The combined ethereal and dioxan solutions, concentrated by distillation under reduced pressure, were stirred into water (1 l.), and the precipitated amine was extracted with ether. Dry hydrogen chloride was passed into the ethereal extract, and the resulting precipitate of crude amine hydrochloride was collected. This pale yellow solid, which did not crystallise from any of the common solvents, was shaken with warm water (100 ml.), and the mixture was filtered. Sodium hydrogen carbonate (2% solution) was added to the filtrate until no more precipitation occurred. The mixture was extracted with ether. Passage of dry hydrogen chloride into the dried ethereal extract caused precipitation of the *amine hydrochloride*. This salt, which was discoloured, does not melt below 300° but chars when heated (Found: C, 73·7; H, 9·2; N, 6·0; Cl, 8·0. $C_{30}H_{44}N_2,HCl,H_2O$ requires C, 74·0; H, 9·7; N, 6·0; Cl, 7·6%). (ii) A solution of 24-aminocholan-3-one hydrochloride (0·1 g.) and phenylhydrazine (0·1 g.) in ethanol (30 ml.) containing hydrochloric acid (*d* 1·18; 0·1 ml.) was boiled under reflux for 30 min. More hydrochloric acid (4N; 10 ml.) was added to the reactants, which were then boiled for a further hour before they were concentrated to a small volume and stirred into iced water (30 ml.). The precipitate which was filtered off did not crystallise from any of the common solvents. The infrared spectrum of the compound appeared to be identical with that of the amine hydrochloride prepared by method (i).

7α : 12α-Diacetoxyindolo(2′ : 3′-3 : 4)chol-3-enic Acid.—Methyl 7α : 12α-diacetoxy-3-oxocholanate [22] (1·2 g.) and phenylhydrazine (1 g.) were heated with glacial acetic acid (50 ml.) on a water-bath for 1 hr., and then stirred into iced water (300 ml.) containing hydrochloric acid (*d* 1·18; 5 ml.). The precipitate (1·25 g.) was filtered off and crystallised (carbon) from benzene–light petroleum to afford *methyl 7α : 12α-diacetoxyindolo(2′ : 3′-3 : 4)chol-3-enate* (0·98 g.) in needles, m. p. 238·5—240°, $[\alpha]_D$ +218° (in chloroform) (Found: C, 72·7; H, 8·1; N, 2·5. $C_{38}H_{47}O_6N$ requires C, 72·8; H, 8·2; N, 2·4%). A solution of the methyl ester (0·3 g.) and potassium hydroxide (16 g.) in 1 : 1 aqueous methanol (80 ml.) was boiled under reflux for 4 hr., diluted with water, and then concentrated under reduced pressure. Subsequent acidification with dilute hydrochloric acid yielded a precipitate, which crystallised from aqueous ethanol to give needles (0·28 g.) of *7α : 12α-dihydroxyindolo(2′ : 3′-3 : 4)chol-3-enic acid*, m. p. 172°, resolidifying and remelting at 210—212° (Found: C, 72·8; H, 8·8. $C_{30}H_{41}O_4N,H_2O$ requires C, 72·4; H, 8·7%).

Acetylation of 7α : 12α-Dihydroxyindolo(2′ : 3′-3 : 4)chol-3-enic Acid (cf. ref. 9).—Perchloric acid (0·1 ml.) was added to a mixture of 7α : 12α-dihydroxyindolo(2′ : 3′-3 : 4)chol-3-enic acid (0·14 g.), acetic anhydride (1·5 ml.) and acetic acid (5 ml.) at 18°. After 30 min. at <30° the reactants were cooled to 18° and ice was added. The mixture was then stirred into water, and the precipitate (0·15 g.), m. p. 247—257° (decomp.), was filtered off. Crystallisation from aqueous ethanol gave needles of *7α : 12α-diacetoxy-N-acetylindolo(2′ : 3′-3 : 4)chol-3-enic acid*, m. p. 260—263° (decomp.) (Found: C, 70·8; H, 7·7. $C_{38}H_{47}O_7N$ requires C, 71·4; H, 7·8%).

Methyl 7α : 12α-Diacetoxy-N-acetylindolo(2′ : 3′-3 : 4)chol-3-enate (cf. ref. 9).—(i) Methyl 7α : 12α-diacetoxyindolo(2′ : 3′-3 : 4)chol-3-enate was treated with acetic acid, acetic anhydride, and perchloric acid. The product, isolated in the usual manner, crystallised from aqueous ethanol to yield *methyl 7α : 12α-diacetoxy-N-acetylindolo(2′ : 3′-3 : 4)chol-3-enate* in needles, m. p.

[22] Jones, Webb, and Smith, *J.*, 1949, 2164.

222—224° (Found: C, 71·2; H, 7·9. $C_{27}H_{40}O_7N$ requires C, 71·7; H, 7·9%). (ii) 7α : 12α-Diacetoxy-*N*-acetylindolo(2′ : 3′-3 : 4)chol-3-enic acid was esterified with diazomethane in ether. Crystallisation of the product from aqueous ethanol afforded needles, m. p. 222—224°, undepressed when mixed with the *N*-acetyl derivative prepared by method (i). The products have identical infrared absorption spectra.

Reaction between Dehydroepiandrosterone and Phenylhydrazine.—(i) Dehydro*epi*androsterone (0·3 g.) and phenylhydrazine (0·3 g.) were heated together in glacial acetic acid (20 ml.) on a boiling-water bath for 1 hr. The mixture was kept for 1 hr. at room temperature before it was stirred into iced water (200 ml.) containing hydrochloric acid (*d* 1·18; 2 ml.). The precipitated solid crystallised from benzene–light petroleum, to give yellow needles (0·13 g.) of 17ξ-*hydroperoxy*-17ξ-*phenylazoandrost*-5-*en*-3β-*ol*, m. p. 151—151·5° (decomp.) (Found: C, 73·8; H, 8·2; N, 7·3. $C_{25}H_{34}O_3N_2$ requires C, 73·2; H, 8·3; N, 6·8%). The crystals darkened on exposure to light and the atmosphere. (ii) A solution of dehydro*epi*androsterone (0·2 g.) and phenylhydrazine (0·1 g.) in ethanol (30 ml.) containing concentrated hydrochloric acid (0·1 ml.) was boiled under reflux for 30 min., and then evaporated. The residual jelly crystallised from aqueous ethanol in needles (0·16 g.), m. p. 128—141°, which, when recrystallised from the same solvent, were tinted yellow (Found: C, 75·4; H, 9·1. Calc. for $C_{25}H_{34}ON_2$: C, 79·3; H, 9·0. Calc. for $C_{25}H_{32}ON_2{\cdot}O{\cdot}OH$: C, 73·2; H, 8·3%). The crystals are probably a mixture of the phenylhydrazone and 17ξ-hydroperoxy-17ξ-phenylazoandrost-5-en-3β-ol. The latter compound, m. p. 151—151·5°, was obtained when the mixture was repeatedly crystallised from ethanol.

Reaction between Dehydroepiandrosterone Acetate and Phenylhydrazine.—Concentrated hydrochloric acid (0·2 ml.) was added to a solution of dehydro*epi*androsterone acetate (2·5 g.) and phenylhydrazine (2 g.) in ethanol (80 ml.) at 70°. When crystals began to be formed, the mixture was cooled and then filtered. The crystalline precipitate (2·1 g.), m. p. 177—178° (decomp.), by rapid recrystallisation from ethanol, afforded colourless needles (1·8 g.) of *dehydroepiandrosterone acetate phenylhydrazone*, m. p. 137—142° (decomp.), $[\alpha]_D$ +37° (in dioxan) (Found: C, 76·5; H, 8·6. $C_{27}H_{36}O_2N_2$ requires C, 77·1; H, 8·6%), $\lambda_{max.}$ 272 mμ (log ε 4·34) in dioxan. The infrared absorption spectrum of the product of m. p. 177—178° and that of the phenylhydrazone, m. p. 137—142°, were identical.

17ξ-*Hydroperoxy*-17ξ-*phenylazoandrost*-5-*en*-3β-*yl Acetate.*—(i) The phenylhydrazone, prepared as above, gave on repeated recrystallisation from benzene–light petroleum yellow leaflets of 17ξ-*hydroperoxy*-17ξ-*phenylazoandrost*-5-*en*-3β-*yl acetate*, m. p. 154·4—155° (decomp.), $[\alpha]_D$ −118° (in dioxan) (Found: C, 71·7; H, 8·1; N, 6·75. $C_{27}H_{36}O_4N_2$ requires C, 71·7; H, 8·0; N, 6·2%), $\lambda_{max.}$ 269, 419 mμ (log ε 4·1, 2·2), $\lambda_{min.}$ 347 mμ (log ε 1·4). The crystals darkened when exposed to light and the atmosphere. (ii) Oxygen was bubbled for 2 hr. *via* a sintered-glass sparger into a solution of dehydro*epi*androsterone acetate phenylhydrazone (1 g.) in benzene (150 ml.) which contained benzoyl peroxide (10 mg.). The solution became yellow and, finally, deep red. Benzene (approx. 100 ml.) was distilled off until precipitation occurred from the solution. The mixture was then cooled, and the hydroperoxide (0·76 g.) was isolated. It crystallised from ethanol in yellow leaflets, m. p. and mixed m. p. with the compound prepared by method (i), 154·5—155° (decomp.). The products have identical infrared absorption spectra.

17ξ-*Phenylazoandrost*-5-*en*-3β-*ol.*—(i) A solution of 17ξ-hydroperoxy-17ξ-phenylazoandrost-5-en-3β-yl acetate (0·2 g.) in dry ether (75 ml.) was added dropwise to a boiling solution of lithium aluminium hydride (0·2 g.) in ether (50 ml.). This mixture was boiled under reflux for 2 hr. and the product of the reduction was isolated, as previously described, as a pale yellow solid, which crystallised from ethanol in needles (0·16 g.) of 17ξ-*phenylazoandrost*-5-*en*-3β-*ol*, m. p. 214—216°, $[\alpha]_D$ −8° (in dioxan) (Found: C, 79·2; H, 9·0; N, 7·2. $C_{25}H_{34}ON_2$ requires C, 79·3; H, 9·0; N, 7·4%), $\lambda_{max.}$ 267, 409 mμ (log ε 4·0, 2·2), $\lambda_{min.}$ 332 mμ (log ε 0·93) in dioxan. (ii) 17ξ-Hydroperoxy-17ξ-phenylazoandrost-5-en-3β-ol (0·4 g.), in a sintered-glass crucible in a Soxhlet extractor, was reduced for 3 hr. with lithium aluminium hydride (0·5 g.) in boiling ether (200 ml.). The product, which was isolated as in method (i), on crystallisation from ethanol, furnished 17ξ-phenylazoandrost-5-en-3β-ol in needles (0·3 g.), m. p. and mixed m. p. with the compound prepared by method (i), 214—216°.

Acetylation of 17ξ-*Phenylazoandrost*-5-*en*-3β-*ol.*—(i) *With acetic anhydride–pyridine mixtures.* The azo-steroid (100 mg.) was kept for 24 hr. at room temperature in a mixture of pyridine (5 ml.) and acetic anhydride (5 ml.). Sufficient ice was added to destroy the anhydride, and

then the mixture was stirred into water (100 ml.). The resulting precipitate crystallised from ethanol to give 17ξ-*phenylazoandrost-5-en-3β-yl acetate* (75 mg.), pale yellow needles, m. p. 173—174° (Found: C, 77·4; H, 8·4. $C_{27}H_{36}O_2N_2$ requires C, 77·1; H, 8·6%). (ii) *With acetic acid–acetic anhydride–perchloric acid* (cf. ref. 9). Perchloric acid (50%; 1 drop) was added to a solution of the azo-steroid (100 mg.) in acetic acid (10 ml.) and acetic anhydride (3 ml.). After 30 min. at >30°, the reactants were cooled and sufficient ice was added to destroy the anhydride. The mixture was then stirred into water (100 ml.), and the resulting precipitate (0·1 g.) was collected. Rapid crystallisation of the product from ethanol gave colourless needles, m. p. 135—140°, having an infrared spectrum identical with that of dehydro*epi*androsterone acetate phenylhydrazone.

Hydrolysis of 17ξ-*Phenylazoandrost-5-en-3β-ol.*—Concentrated hydrochloric acid (5 ml.) was added to a solution of the azo-steroid (0·1 g.) in ethanol (20 ml.). This solution was boiled under reflux for 1 hr.; it became deep crimson and then the colour faded. After the solution had been kept overnight at room temperature it was poured into water. The resulting precipitate was crystallised, with difficulty, from dilute methanol to give prisms, m. p. 149—151°. The m. p. was undepressed when the compound was mixed with an authentic specimen of dehydro*epi*androsterone, and the compound has an infrared spectrum which is identical with that of the keto-steroid.

*Attempted Conversion of Dehydro*epi*androsterone Acetate Phenylhydrazone into an Indolosteroid.*—(i) The phenylhydrazone (100 mg.) in glacial acetic acid (20 ml.) was heated for 1 hr. on a boiling-water bath and then added to dilute hydrochloric acid, and filtered. Crystallisation from ethanol gave dehydro*epi*androsterone acetate phenylhydrazone (85 mg.), m. p. 135—145°. (ii) A solution of the phenylhydrazone (100 mg.) in glacial acetic acid (50 ml.) was boiled under reflux for 18 hr., then poured into dilute hydrochloric acid (200 ml.). Crystallisation from ethanol gave dehydro*epi*androsterone acetate phenylhydrazone, m. p. 137—142°. (iii) A solution of the phenylhydrazone (100 mg.) in ethanol (40 ml.) containing concentrated hydrochloric acid (10 ml.) was boiled under reflux for 1 hr. The mixture was then stirred into water (100 ml.) and kept overnight. Crystallisation of the precipitate from dilute methanol gave dehydro*epi*androsterone, m. p. 142—143°. The phenylhydrazone was recovered unchanged after being shaken with cold dilute hydrochloric acid for 10 min.

Thanks are accorded to Professor H. B. Henbest for a gift of 3β-hydroxychol-5-enic acid, and to the Department of Scientific and Industrial Research for a Maintenance Award (for A. F. C.).

KING'S COLLEGE (UNIVERSITY OF LONDON),
STRAND, LONDON, W.C.2.

[*Received, February 11th,* 1959.]

---

650. *Diazaindenes and Their Quaternary Salts. Part I. The Preparation of* 2,3,3-*Trimethyl*-3H-1,7-*diazaindene, and its Methiodides and Derived Cyanine Dyes.**

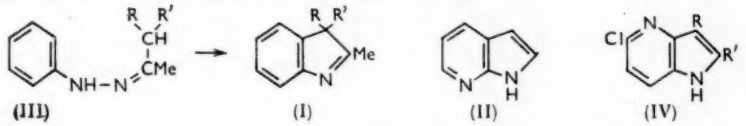
By G. E. FICKEN and J. D. KENDALL.

A Fischer indole synthesis with isopropyl methyl ketone 2-pyridylhydrazone gives 2,3,3-trimethyl-3*H*-1,7-diazaindene, which with methyl iodide yields largely the 7-methiodide. The isomeric 1-methiodide has been synthesised by way of 1,3,3-trimethyl-2-methylene-1,7-diazaindane. The methiodides yield two series of cyanine dyes, the light absorption of which is discussed.

3,3-DIALKYL-2-METHYL-3*H*-INDOLES (I) form quaternary salts which possess reactive methyl groups in the 2-position. They have consequently been frequently used for the preparation of cyanine and merocyanine dyes, the first recorded instance being König's synthesis of the symmetrical trimethincyanine from 1,2,3,3-tetramethyl-3*H*-indolium iodide

* A preliminary account was given at the VIII National Congress of the Società Chimica Italiana held jointly with the Society of Chemical Industry at Turin, May, 1958.

and ethyl orthoformate.[1] We have investigated the preparation of aza-analogues of (I) containing one nitrogen atom in each ring. A number of bases of this type, and derivatives thereof, have been described; *e.g.*, Robison and Robison [2] synthesised the base (II). However, as these all lack the characteristic *gem*-dialkyl group, the nitrogen atom of the five-membered ring carries a hydrogen atom, as in the true indoles.



(III) (I) (II) (IV)

3*H*-Indoles are generally prepared by Fischer's method [3] from a phenylhydrazone of type (III), cyclisation occurring on to the tertiary carbon atom in preference to the methyl group. Little has been reported, however, on the use of hydrazones of the heterocyclic series. However, the 2-chloro-5-pyridylhydrazones of acetone and propionaldehyde were reported to yield the chlorodiazaindenes (IV; R = H, R′ = Me and *vice versa* respectively) when heated with zinc chloride; [4] Clemo and Holt [5] cyclised cyclohexanone 2-methyl-3-pyridylhydrazone in low yield by zinc chloride; and Okuda and Robison [6] recently used polyphosphoric acid for the cyclisation of the 2-pyridylhydrazones of cyclohexanone and deoxybenzoin to diazaindenes. The present paper deals with the cyclisation of 2-pyridylhydrazones, and a later paper will describe the use of 3- and 4-pyridylhydrazones.

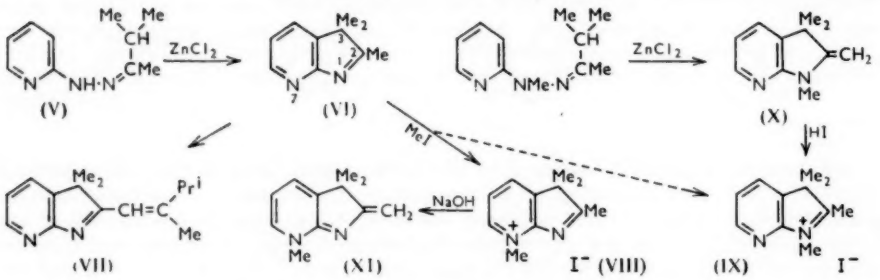
Okuda and Robison [6] obtained negative results with the 2-pyridylhydrazones of acetaldehyde, acetone, and pyruvic acid, as did Fargher and Furness [7] with acetone and propionaldehyde 2-pyridylhydrazones. We find, however, that heating isopropyl methyl ketone 2-pyridylhydrazone (V) with a catalytic amount of zinc chloride gives a mixture from which 2,3,3-trimethyl-3*H*-1,7-diazaindene (VI) can be isolated. Also formed in the reaction were 2-aminopyridine and a higher-boiling material, apparently possessing structure (VII). Compound (VII) could not be purified; it had evidently arisen by reaction of the diazaindene (VI) with unchanged pyridylhydrazone (V) under the action of the zinc chloride, 2-pyridylhydrazine being eliminated. The evidence for structure (VII) is discussed below. The mechanism of the Fischer synthesis (discussed in ref. 3) is generally considered to involve an electrophilic attack at the carbon atom adjacent to that carrying the –NH–N= group. In keeping with this, and with the well-known inertness of pyridines towards electrophilic substitution,[8] it was found that a considerably higher temperature (250°) was needed for the formation of the diazaindene (VI) than for that of 2,3,3-trimethyl-3*H*-indole (I; R = R′ = Me), which is formed from isopropyl methyl ketone phenylhydrazone and zinc chloride in refluxing ethanol.[9] Okuda and Robison [6] reported similar difficulty in cyclisation of 2-pyridylhydrazones with polyphosphoric acid.

The base (VI) with methyl iodide gave a mixture from which the 7-methiodide (VIII) was isolated as the major product; an ethiodide was also obtained. The position of quaternisation was proved by an unambiguous synthesis of the 1-methiodide (IX): *N*-methyl-*N*-2-pyridylhydrazine was synthesised, both by a modification of Tschitschibabin and Knunjanz's method [10] involving reduction of 2-(methylnitrosoamino)pyridine, and by

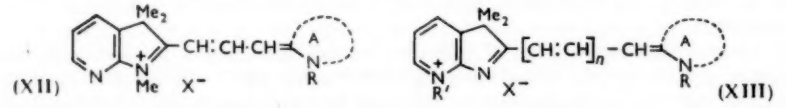
[1] König, *Ber.*, 1924, **57**, 685.
[2] Robison and Robison, *J. Amer. Chem. Soc.*, 1955, **77**, 457.
[3] (*a*) Elderfield, "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, 1952, Vol. III, Chapter 1; (*b*) Sumpter and Miller, "The Chemistry of Heterocyclic Compounds," Interscience Publ. Inc., New York, 1954, Vol. VIII, p. 3.
[4] Deutsche Gold-und Silberscheideanstalt, B.P. 259,982/1925.
[5] Clemo and Holt, *J.*, 1953, 1313.
[6] Okuda and Robison, *J. Amer. Chem. Soc.*, 1959, **81**, 740.
[7] Fargher and Furness, *J.*, 1915, **107**, 688.
[8] Elderfield, *op. cit.*, 1950, Vol. I, p. 401—410.
[9] Plancher, *Ber.*, 1898, **31**, 1488.
[10] Tschitschibabin and Knunjanz, *Ber.*, 1928, **61**, 2216.

XUM

reaction of 2-chloropyridine with methylhydrazine; reaction of 2-methylaminopyridine with chloramine [11] was unsuccessful, the amine being recovered. The *N*-methyl-*N*-2-pyridylhydrazone of isopropyl methyl ketone, with zinc chloride, gave 1,3,3-trimethyl-2-methylene-3*H*-1,7-diazaindane (X). As the anhydro-base of the 1-methiodide (IX), it



added hydrogen iodide to give this quaternary salt, which differed from that obtained by quaternisation of the base (VI). Both methiodides had reactive methyl groups and they gave different series of cyanine and merocyanine dyes, *e.g.*, (XII) and (XIII; R′ = Me).



Both methiodides gave symmetrical trimethincyanines on reaction with ethyl orthoformate in pyridine. Apart from the difference in light absorption between corresponding dyes of the two series (to be discussed later), the most striking difference between the two series is the brilliant fluorescence of solutions of trimethincyanines of structure (XIII; $n = 1$). The monomethincyanines and merocyanines from the 7-methiodide, and all of the dyes from the 1-methiodide, fluoresce only feebly or not at all in solution.

Although the 1-methiodide (IX) could not be isolated from the product of quaternisation of base (VI), the presence of 5—10% of it was proved by reaction of the crude mixture with *p*-dimethylaminobenzaldehyde followed by chromatographic separation of the mixture of dyes. Formation of the 7-methiodide (VIII) preponderantly on quaternisation of the diazaindene (VI) implies that $N_{(7)}$ is more basic than $N_{(1)}$, in agreement with the known stronger basicity of pyridines than of 3*H*-indoles. Robison and Robison [12] showed that 1,7-diazaindene (II) reacts with methyl iodide exclusively on the nitrogen atom of the six-membered ring, but here the difference in basicity of the two nitrogen atoms (a pyridine and a virtually non-basic indole nitrogen) would be much more marked.

Table 1 gives some light absorptions for our compounds. Compared with 2,3,3-trimethyl-3*H*-indole, the diazaindene shows a bathochromic shift of the main absorption band of 23 mμ. The 1-methiodide (IX) shows a new absorption band at 317 mμ which is not present in the structurally similar tetramethyl-3*H*-indolium iodide. The main absorption maximum (277 mμ) of the latter corresponds, as expected, with the band at 274 mμ in the spectrum of trimethyl-3*H*-indole in acid solution. Likewise, in the case of diazaindene (VI), the spectrum in acid solution resembles quite closely that of the 7-methiodide, whilst the 1-methiodide has a rather different spectrum. This indicates that protonation of the base occurs largely on the pyridine-nitrogen atom, in agreement with the quaternisation. The spectrum of tetramethyl-3*H*-indolium iodide in alkaline solution,

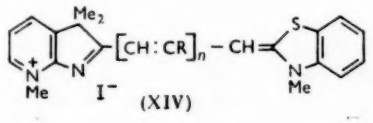
[11] Cf. Diamond and Audrieth, *J. Amer. Chem. Soc.*, 1955, **77**, 3131.
[12] Robison and Robison, *ibid.*, p. 6554.

TABLE 1. *Absorption spectra,* $\lambda_{max.}$ (mμ) *and* log ε *for ethanolic solutions (inflections in parentheses).*

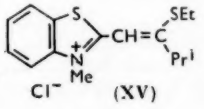
	Neutral			Acid (HCl)		
2,3,3-Trimethyl-3*H*-indole	257			226	274	
	3·76			3·78	3·72	
The diazaindene (VI)	245	280		240	(282)	300
	3·61	3·87		3·75	(3·76)	3·89
	Alkaline (NaOH)			Neutral		
1,2,3,3-Tetramethyl-3*H*-indolium iodide		278	(308)		277	(299)
		4·34	(3·40)		3·97	(3·49)
The diazaindene 1-methiodide (IX)	249	274	313	248	274	317
	3·87	4·02	3·72	3·79	4·02	3·79
The diazaindene 7-methiodide (VIII)		293	345	362 (245)	(285)	304
		4·02	3·47	3·48 (3·66)	(3·76)	3·86

i.e., effectively a solution of 1,3,3-trimethyl-2-methyleneindoline (" Fischer's base "), is rather similar to that of the neutral solution, apart from a greater intensity of the main absorption band. The diazaindene 1-methiodide likewise shows little change of spectrum in alkaline solution, where the change (IX ⟶ X) presumably occurs. On the other hand, addition of alkali to a solution of the 7-methiodide results in a yellow coloration, due to the appearance of two new absorption bands above 300 mμ. This yellow colour, discharged by addition of excess of acid, must be ascribed to the formation of the methylene base (XI), which possesses an *ortho*-quinonoid pyridine ring.

To prove the structure (VII) assigned to the high-boiling by-product arising in the preparation of the diazaindene, the crude material was treated successively with methyl iodide and 3-methyl-2-methylthiobenzothiazolium iodide. The mixture of dyes obtained was separated chromatographically into the methincyanine (XIV; $n = 0$), derived from methiodide (VIII), and the trimethincyanine (XIV; R = Pr^i, $n = 1$), spectroscopically



(XIV)



(XV)

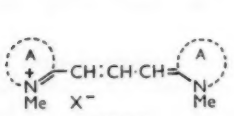
closely similar to dye (XIV; R = H, $n = 1$). The structure of the new dye was proved by the following unambiguous synthesis. Reaction of 2,3-dimethylbenzothiazolium toluene-*p*-sulphonate with isobutyryl chloride in pyridine,[13] and of the resulting 3-methyl-2-isobutyrylmethylenebenzothiazoline with ethanethiol in methanolic hydrogen chloride [14] gave the quaternary salt (XV). The use of intermediates of type (XV) for the preparation of trimethincyanines was first described by the I.G. Farbenindustrie; [15] reaction of the salt (XV) with the 7-methiodide (VIII) gave dye (XIV; R = Pr^i, $n = 1$), identical with that from (VII).

Light Absorption of the Dyes.—Amongst the dyes prepared were a number of trimethincyanines (XII; R = Me) and (XIII; $n = 1$, R = R′ = Me) from the 3- and 4-methiodide respectively. The light-absorption data for these are given in Table 2(*b*), together with the figures for the symmetrical trimethincyanines (XVI) (only the principal maximum is given in each case, although most of the dyes possess a smaller maximum or inflection on the short-wavelength side of the principal maximum). In part (*a*) of the Table, data are given for the dimethincyanines (XVII and XVIII; B = 1,3,3- and 3,3,7-trimethyl-3*H*-1,7-diazaindene-2), for which the corresponding symmetrical dyes are (XIXa and b). The calculated value for each unsymmetrical dye is given, being the arithmetic mean of the

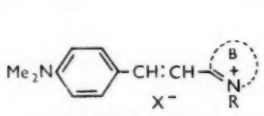
[13] Cf. Brooker, White, and Eastman Kodak Co., U.S.P. 2,112,139/1938.
[14] Cf. Gevaert Photo-Producten N.V., B.P. 637,182/1950.
[15] I.G. Farbenindustrie A.G., B.P. 412,309/1932.

XUM

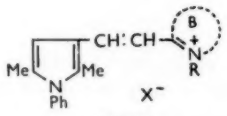
wavelengths for the corresponding symmetrical dyes (XVI or XIX) and (XX or XXI). The difference between this calculated average and the observed value, the " deviation " of the dye, has been correlated by Brooker *et al.*[16,17,18] with the relative basicities of the heterocyclic nuclei. Table 2 (in which the nuclei in the first column are arranged in order of increasing basicity) shows that the deviations are small for the 7-methyldiazaindene nucleus in combination with nuclei from benzoxazole onwards. It follows therefore from Brooker's investigations [18] that $N_{(7)}$ in the diazaindene is itself strongly basic. In fact, the deviations obtained with the dyes of structure (XVII) and (XVIII) indicate that $N_{(7)}$ is intermediate in basicity between benzothiazole and β-naphthothiazole. The 1-quaternised diazaindene nucleus on the other hand gives large deviations in combination with the more basic nuclei, from which it appears to lie between nuclei (XXII) and



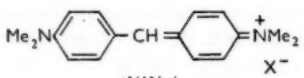
(XVI)



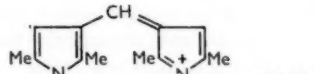
(XVII)



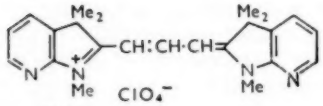
(XVIII)



(XIXa)

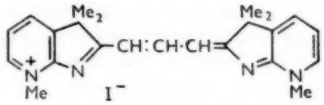


(XIXb)



(XX)

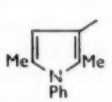
$\lambda_{max.}$ 5360 Å, log ε 5·15



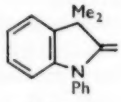
(XXI)

$\lambda_{max.}$ 6085 A, log ε 5·13

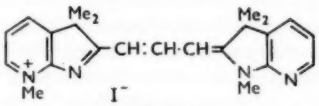
(XXIII) in the basicity series. These facts are brought out in Table 3, where the deviations obtained from Table 2 are compared with Brooker's values [16,18] for a number of unsymmetrical cyanines not containing the diazaindene nucleus. The majority of these are trimethincyanines, but the dyes possessing styryl or pyrrole nuclei are dimethincyanines of type (XVII) and (XVIII). It is of interest that the unsymmetrical diazaindene trimethincyanine (XXIV) shows a considerable deviation, which is consistent with the



(XXII)



(XXIII)



(XXIV)

$\lambda_{max.}$ 5580 Å, log ε 4·95

other values given in Table 3. This dye was prepared by reaction of the 7-methiodide (VIII) with ethyl trithio-orthoformate to give an intermediate of the type described by Kendall and Majer,[19] which then reacted with the 1-methiodide (IX) to give dye (XXIV).

It should be noted that, except for nuclei (XXII) and (XXIII), Brooker's values refer to *N*-ethyl dyes, whereas the deviations for the diazaindene dyes refer to *N*-methyl dyes. Nevertheless, replacement of methyl by ethyl does not generally affect the wavelength

[16] Brooker, Sklar, Cressman, Keyes, Smith, Sprague, Van Lare, Van Zandt, White, and Williams, *J. Amer. Chem. Soc.*, 1945, **67**, 1875.
[17] Brooker and Sprague, *ibid.*, p. 1869.
[18] Brooker, Sprague, and Cressman, *ibid.*, p., 1889.
[19] Kendall and Majer, *J.*, 1948, 687.

of maximum absorption by more than about 50 Å, so that the position of the diazaindene nitrogen atoms in the basicity series would not be significantly affected, since this position was determined by those dyes which gave the largest deviations.

Some facts of interest emerge from the above results:

TABLE 2. *Light absorption data for dye iodides* [$\lambda_{max.}$ (Å) *and* log ε].

(a) *Dimethincyanines.*

Formula	Symmetrical dye (XIX)	B = 1,3,3-Trimethyl-1,7-diazaindene obs.	B = 1,3,3-Trimethyl-1,7-diazaindene calc.	B = 3,3,7-Trimethyl-1,7-diazaindene obs.	B = 3,3,7-Trimethyl-1,7-diazaindene calc.
(XVII)	6100 [b]	5590	5730	5390	6095
		4·84		4·78	
(XVIII)	4485 [a]	4845 [a]	4925	4760 [a]	5285
		4·62		4·76	

(b) *Trimethincyanines.*

Nucleus A	Symmetrical dye (XVI)	1,3,3-Trimethyl dye (XII) obs.	1,3,3-Trimethyl dye (XII) calc.	3,3,7-Trimethyl dye (XIII; R′ = Me, *n* = 1) obs.	3,3,7-Trimethyl dye (XIII; R′ = Me, *n* = 1) calc.
1,3,3-Trimethyl-3*H*-indole-2- [a]	5465 [d]	5400	5415	5715	5775
	5·18	5·05		5·14	
3-Methyl-2-benzoxazole	4840 [a]	4980	5100	5485	5465
	4·97	4·84		5·22	
3-Methyl-2-benzothiazole	5580 [a]	5315	5470	5850	5835
	5·09	4·99		5·25	
3-Methylnaphtho[1′,2′:4,5]thiazole-2-	5980 [f]	5360	5670	6020	6035
	5·12	4·90		5·16	
1-Methyl-2-quinoline	6050 [g]	5400	5705	6060	6070
	5·24	4·93		5·08	
1-Methyl-4-quinoline	7070 [h]	5700	6215	6510	6580
	5·35	4·79		4·99	

[a] Perchlorates. [b] Brooker, Sklar, Cressman, Keyes, Smith, Sprague, Van Lare, Van Zandt, White, and Williams, *J. Amer. Chem. Soc.*, 1945, **67**, 1875. [c] Brooker and Sprague, *ibid.*, p. 1869. [d] Hamer (*J.*, 1927, 2796) gives 5480 Å for the iodide. [e] König and Meier (*J. prakt. Chem.*, 1925, **109**, 324) give 4850 and 5580 Å respectively for these dyes. [f] Toluenesulphonate; Hamer (*J.*, 1929, 2598) gives 6000 Å for the iodide. [g] Brooker and Sprague (*J. Amer. Chem. Soc.*, 1941, **63**, 3203) give 6040 Å. [h] Hamer (*J.*, 1927, 2796) gives 7150 Å.

TABLE 3. *Deviations* (Å) *of dyes.*

Nucleus	1-Diaza	(XXIII)	Indo	Oxa	Thia	7-Diaza	Naphtho	2-Quino	4-Quino
(XVII)	140	170	290	455	555	705	720	820	1125
(XVIII)	80	140	260	345	375	525	540	525	730
1-Diaza [a]	(0)	—	15	120	155	145	310	305	515
(XXIII)		(0)	30	110	145	—	180	255	380
Indo [b]			(0)	65	100	60	110	145	220
Oxa [b]				(0)	0	−20	30	15	0
Thia [b]					(0)	−15	−5	30	15
7-Diaza [a]						(0)	15	10	70
Naphtho [b]							(0)	20	−20
2-Quino [b]								(0)	−5
4-Quino [b]									(0)

[a] 1,3,3-Trimethyl-1,7-diazaindene-2 and 3,3,7-trimethyl-1,7-diazaindene-2 respectively. [b] 3,3-Dimethyl-3*H*-indole-2-, 2-benzoxazole, 2-benzothiazole, naphtho(1′,2′:4,5)thiazole-2, 2-quinoline and 4-quinoline (all with an *N*-methyl or *N*-ethyl group).

First, $N_{(7)}$ in the diazaindene is considerably more basic than $N_{(1)}$, in agreement with the result of quaternisation of the base. Brooker [16] has, however, pointed out that basicities from deviation measurements are not necessarily strictly equivalent to the true basicities given by p*K* values, and in fact prefers to replace the basicities from deviations by the term "N^{IV}–N^{III} stabilisation." This implies that the 7-quaternised diazaindene displays less tendency to pass into a structure bearing a tervalent nitrogen atom than does the 1-quaternary salt. This is clearly related to the formation of an unstable *ortho*-quinonoid pyridine ring in the N^{III} form of the 7-methyl dyes, as in the methylene base (XI).

Secondly, $N_{(1)}$ and $N_{(7)}$ in the diazaindene are less basic than 3*H*-indole and pyridine respectively, pyridine being above all the nuclei shown in Table 3 in the basicity series.

This appears to be an instance of the well-known lowering of the basicity of a nitrogen heterocycle by the introduction of further nitrogen atoms (cf. Albert [20]).

Experimental

2-Hydrazinopyridine.—This was prepared by the method of Fargher and Furness.[7] The *p-nitrobenzylidene derivative* formed yellow needles, m. p. 241·5—242°, from ethanol (Found: C, 59·6; H, 4·4. $C_{13}H_{10}O_2N_4$ requires C, 59·5; H, 4·2%).

2,3,3-Trimethyl-3H-1,7-diazaindene (VI).—2-Hydrazinopyridine (77·0 g.), isopropyl methyl ketone (80 ml.), and benzene (250 ml.) were refluxed together, the water being removed by azeotropic distillation. The hydrazone remaining after distillation of the solvent was heated at 250° with anhydrous zinc chloride (2·0 g.) until ammonia evolution ceased (1 hr.). The dark brown product was fractionated under reduced pressure to give (i) b. p. 100°/17 mm. to 148°/21 mm. (14·4 g.), (ii) b. p. 112—120°/0·8 mm. (51·8 g.), and (iii) b. p. 130—200°/2 mm. (8·6 g.); all three fractions partially solidified on cooling. Fraction (i) consisted largely of 2-aminopyridine, m. p. and mixed m. p. 56—57° (from ethyl acetate); the methiodide had m. p. and mixed m. p. 152—153° (Tschitschibabin, Konowalowa, and Konowalowa [21] give m. p. 145—150°). Fraction (ii) crystallised from cyclohexane to give a solid (33·0 g.), m. p. 62—65°, further quantities of less pure material being obtained from the mother-liquors. Repeated recrystallisation from cyclohexane gave *2,3,3-trimethyl-3H-1,7-diazaindene* as colourless needles, m. p. 77·5—78° (Found: C, 74·7; H, 7·5; N, 17·6. $C_{10}H_{12}N_2$ requires C, 75·0; H, 7·5; N, 17·5%). The compound slowly darkened and the m. p. fell several degrees during a year. Fraction (iii) of the distillation was a mixture, containing some of the diazaindene, but no pure material could be obtained from it.

The diazaindene (11·5 g.) was refluxed in acetone (50 ml.) with methyl iodide (9·0 ml.) for 1 hr. The solid (12·5 g.) which separated had m. p. 214—215° (decomp.); the *7-methiodide* formed colourless prisms, m. p. 218—219° (decomp.), by crystallisation from propan-2-ol (Found: I, 41·8. $C_{11}H_{15}N_2I$ requires I, 42·0%). The mother-liquors on evaporation deposited a further crop (1·9 g.) of less pure material, and the final filtrate consisted of a mixture of the 1- and the 7-methiodide. Reaction of the base with ethyl iodide gave the 7-ethiodide as a deliquescent solid, m. p. 138—142°, which could not be recrystallised.

2-(Methylnitrosoamino)pyridine.—2-Aminopyridine (212 g.) was methylated with sodamide and dimethyl sulphate, according to the intructions of Tschitschibabin and Knunjanz;[10] purification *via* the benzoyl derivative was however unnecessary. Instead, the crude methylation product dissolved in concentrated hydrochloric acid (725 ml.) and water (390 ml.) was treated dropwise, with stirring, with an aqueous solution of sodium nitrite (130 g.), the temperature being kept below 10°. After the solution at room temperature had been stirred for 1 hr., excess of ammonia was added, the oil was separated and the aqueous solution was extracted three times with ether. After drying (K_2CO_3) of the combined extracts, the ether was removed and the product distilled. A fraction (21 g.), b. p. 70—90°/18 mm., was followed by the main fraction, b. p. 106—110°/12 mm., consisting of the nitrosamine (84 g., 27%); the picrate had m. p. 194—195° (Tschitschibabin and Knunjanz [10] give b. p. 123—124°/30 mm., yield 21%, picrate, m. p. 186—187°).

N-Methyl-N-2-pyridylhydrazine.—(a) *From the nitrosamine.* Reduction of the nitrosamine by zinc and acetic acid [10] proved unsatisfactory in our hands, the product appearing to contain large amounts of 2-methylaminopyridine. Reduction with hydrazine and Raney nickel gave this amine exclusively, but lithium aluminium hydride proved satisfactory. A solution of the nitrosamine (33 g.) in dry ether (100 ml.) was added slowly to a stirred solution of lithium aluminium hydride (10 g.) in ether (250 ml.). When the vigorous reaction had subsided, stirring was continued for a further 1 hr., then ethyl acetate (10 ml.) was added, followed by 40% aqueous sodium hydroxide solution (50 ml.). The ether layer was separated and the aqueous layer was extracted once with ether. After drying (K_2CO_3), the combined ether solutions were distilled to yield *N*-methyl-*N*-2-pyridylhydrazine (30·7 g.), b. p. 113—118°/12 mm. (Tschitschibabin and Knunjanz [10] give b. p. 105°/10 mm.); the *p-nitrobenzylidene derivative* formed orange needles, m. p. 137—137·5°, from ethanol (Found: C, 61·15; H, 4·7. $C_{13}H_{12}O_2N_4$ requires C, 60·9; H, 4·7%).

(b) *From methylhydrazine.* Isolation of methylhydrazine from its hydrochloride was found

[20] Albert, *Chem. Soc. Special Publ.* No. 3, 1955, p. 124.
[21] Tschitschibabin, Konowalowa, and Konowalowa, *Ber.*, 1921, **54**, 814.

to be more satisfactory than the method of von Brüning [22] using the sulphate (we are indebted to Mr. D. J. Fry for suggesting this modification). A solution of methylhydrazine sulphate [23] (309 g.) in distilled water (1 l.) was added to a stirred solution of barium chloride dihydrate (525 g.) in warm water (2 l.). After a further hour's warming, the suspension of barium sulphate was filtered through kieselguhr, and the filtrate was evaporated to yield an almost colourless solid. *Methylhydrazine hydrochloride* formed colourless plates, m. p. 122—124°, from ethanol (Found: C, 15·1; H, 8·2; Cl, 43·6. CH_7N_2Cl requires C, 14·6; H, 8·55; Cl, 43·0%). The crude hydrochloride was dissolved in water (500 ml.), and the solution treated cautiously with a large excess of sodium hydroxide (flake), strong cooling being necessary. The oil which separated was poured off, and the aqueous layer (with much suspended sodium chloride) was evaporated at atmospheric pressure. The first 250 ml. of distillate was saturated with potassium carbonate, more oil separating. This was combined with the material obtained previously, dried (K_2CO_3), and distilled at 94—108°/756 mm.; the wide boiling range indicated that the methylhydrazine (72 g.) was still partially hydrated.

This material was refluxed for 48 hr. with 2-chloropyridine (54 g.) and 2-methoxyethanol. After distillation of as much volatile material as possible under reduced pressure on the steam-bath, excess of sodium hydroxide solution was added. The oil was separated and the aqueous layer extracted with ether (3 × 50 ml.). The combined oil and extracts were dried (K_2CO_3) and distilled, *N*-methyl-*N*-2-pyridylhydrazine being obtained at b. p. 116—122°/18 mm. (52·8 g.). The picrate had m. p. 166—167° (Found: C, 41·2; H, 3·7. Calc. for $C_{12}H_{12}O_7N_6$: C, 40·9; H, 3·4%), and the benzylidene derivative, m. p. 67—68° (Tschitschibabin and Knunjanz [10] give m. p.s 153—155° and 67—68° respectively). The *p*-nitrobenzylidene derivative had m. p. 136—137°, undepressed by that obtained from (*a*).

1,3,3-*Trimethyl*-2-*methylene*-1,7-*diazaindane* (X).—*N*-Methyl-*N*-2-pyridylhydrazine (52·5 g.), isopropyl methyl ketone (50 ml.), and benzene (150 ml.) were refluxed together until no more water was removed. The hydrazone was heated at 230° with anhydrous zinc chloride (2·0 g.) for 3 hr. and the product distilled. The material boiling between 73°/0·9 mm. and 130°/1·5 mm. (48·0 g.) was refractionated to give (i) 2-methylaminopyridine, b. p. 93°/14 mm. to 100°/13 mm. (18·0 g.) [picrate, m. p. and mixed m. p. 194—195°; and methiodide, m. p. 159·5—160·5° (Tschitschibabin, Konowalowa, and Konowalowa [21] give m. p.s 190° and 159—160°)]. An intermediate fraction (ii), b. p. 101°/13 mm. to 116°/11 mm. (7·0 g.), was followed by (iii), b. p. 117—120°/11 mm. (18·8 g.) consisting largely of 1,3,3-trimethyl-2-methylene-3*H*-1,7-diazaindane (X), b. p. 118°/12 mm., with a blue fluorescence; it contained a persistent impurity which could not be separated by repeated fractionation (Found: C, 73·95; H, 8·05. Calc. for $C_{11}H_{14}N_2$: C, 75·8; H, 8·1%). The base (6·66 g.) in propan-2-ol (60 ml.) was treated with freshly distilled hydriodic acid (*d* 1·70; 5·5 ml.). The solid which slowly crystallised was washed with a little cold propan-2-ol, and then with ether. The ***hydriodide*** (**2,3,3-*trimethyl*-3H-1,7-*diazaindene* 1-*methiodide***) (7·57 g.) formed colourless needles, m. p. 240·5—241° (decomp.) (from ethanol) (Found: C, 44·0; H, 5·3; N, 9·1; I, 42·6. $C_{11}H_{15}N_2I$ requires C, 43·7; H, 5·0; N, 9·3; I, 42·0%).

Preparation of Diazaindene Dyes.—(a) *Mono- and tri-methincyanines.* The monomethincyanines, listed in Table 4, were prepared by reaction of the diazaindene 7-methiodide (VIII) or -ethiodide with the appropriate 2-methylthio-heterocyclic quaternary iodide in ethanol in the presence of triethylamine. If the cyanine iodide did not separate on cooling, the solution was poured into aqueous sodium perchlorate, and the dye was isolated as the perchlorate. The unsymmetrical trimethincyanines (Tables 5 and 6) were prepared by reaction of the diazaindene 1- or 7-alkiodide with an ω-ethylthiovinyl quaternary toluene-*p*-sulphonate or iodide in ethanol containing triethylamine, or with an ω-acetanilidovinyl quaternary iodide in pyridine; conversion into the perchlorate as above was sometimes necessary. The symmetrical trimethincyanines were prepared by reaction of the diazaindene alkiodide with ethyl orthoformate in pyridine. The yields, where given, refer to the crude and once recrystallised materials.

(b) *Dimethincyanines containing nuclei* (XVII) *and* (XVIII). The diazaindene 1-methiodide (0·60 g.) and *p*-dimethylaminobenzaldehyde (0·30 g.) were refluxed in ethanol (5·0 ml.) containing one drop of piperidine for one hour. The solid (0·35 g.) which separated on cooling was recrystallised from ethanol (12 ml.) to give **2-p-*dimethylaminostyryl*-3,3-*dimethyl*-3H-1,7-*diazaindene* 1-*methiodide*** (0·14 g.) as blue needles, m. p. 264—265° (decomp.) (Found: I, 29·7.

[22] von Brüning, *Annalen*, 1889, **253**, 7.
[23] Hatt, *Org. Synth.*, **16**, 51.

XUM

TABLE 4. (A) (3,3-*Dimethyl*-7-R′-3H-1,7-*diazaindene*-2)*methincyanine dyes* (XIII; $n = 0$).

Nucleus A	R′	X	M. p. (decomp.)	Yield	Solvent [a]	Appearance	$\lambda_{max.}$ (Å)	log $\varepsilon_{max.}$	Formula		Found (%)	Reqd. (%)
1-Methyl-2-quinoline	Me	ClO_4	250—251° [b]	—	GM	Red needles	4990	4·88	$C_{21}H_{23}O_4N_2Cl$	Cl,	8·2	8·5
3,4-Dimethyl-2-thiazole	Et	ClO_4	203—204 [b]	—	E	Pale yellow plates	4470	4·51	$C_{16}H_{20}O_4N_2ClS$	N,	10·1	10·5
3-Methyl-4-phenyl-2-thiazole	Et	ClO_4	289—290	—	M	Yellow prisms	4500	4·82	$C_{21}H_{23}O_4N_2ClS$	N,	9·1	9·1
3-Methyl-2-benzothiazole	Me	I	313—314	47; 29	M	Yellow plates	4530	5·00	$C_{19}H_{19}N_2IS$	N,	9·6	9·35
										I,	27·9	28·25
3-Ethyl-2-benzothiazole	Et	I	318—319	33; 17	M	Yellow prisms, blue reflex	4540	4·99	$C_{21}H_{24}N_2IS$	I,	26·3	26·6

[a] E = Ethanol, G = 2-Ethoxyethanol, M = Methanol. [b] Without decomp.

TABLE 5. (A) (1,3,3-*Trimethyl*-3H-1,7-*diazaindene*-2)*trimethincyanine iodides* (XII).

Nucleus A	M. p. (decomp.)	Yield (%)	Solvent [a] (ml./g.)	Appearance	Formula		Found (%)	Reqd. (%)
1,3,3-Trimethyl-3*H*-indole-2	241—242° [b]	14; 11	E(30)	Purple plates, silver reflex	$C_{24}H_{25}O_4N_2Cl$ [c]	N,	8·8	9·2
1-Methyl-2-quinoline	271—272 [b]	36; 22	M(55)	Green needles	$C_{23}H_{24}N_2I$	I,	26·6	27·0
1-Methyl-4-quinoline	326	64; 44	M(60)	Deep green plates	$C_{23}H_{24}N_2I,H_2O$	I,	25·6	26·0
1,3,3-Trimethyl-3*H*-1,7-diazaindene-2	272—273	33; 19	M(18)	Red plates, blue reflex	$C_{23}H_{27}O_4N_4Cl$ [c]	N,	12·2	12·2
3-Methyl-2-benzoxazole	292—293	39; 32	M(30)	Red-brown plates, blue reflex	$C_{21}H_{22}ON_2I$	I,	27·4	27·6
3-Methyl-2-benzothiazole	260—261	10; 6	M(30)	Green plates	$C_{21}H_{22}N_2IS,\frac{1}{2}H_2O$	C,	51·95	52·1
						H,	5·3	4·8
						I,	25·9	26·2
3-Methylnaphtho(1′,2′:4,5)thiazole-2	211—212 [b]	8; 5	G(50)	Red-brown prisms	$C_{25}H_{24}N_2IS$	I,	24·5	24·2

[a, b] See Table 4. [c] Perchlorate.

TABLE 6. (A) (3,3-*Dimethyl*-7-R′-3H-1,7-*diazaindene*-2)*trimethincyanine iodides* (XIII; $n = 1$).

Nucleus A	R′	M. p. (decomp.)	Yield (%)	Solvent [a] (ml./g.)	Appearance	Formula		Found (%)	Reqd. (%)
1,3,3-Trimethyl-3*H*-indole-2	Me	271—272°	95; 40	M(55)	Brown prisms, blue reflex	$C_{24}H_{25}O_4N_2Cl$ [c]	N,	9·4	9·2
1-Methyl-2-quinoline	Me	250—251	45; —	E	Deep green	$C_{23}H_{24}N_2I$	I,	26·9	27·0
1-Methyl-4-quinoline	Me	297·5—298·5	53; —	M	Blue-green needles	$C_{23}H_{24}N_2I$	I,	26·9	27·0
3,3,7-Trimethyl-3*H*-1,7-diazaindene-2	Me	282	33; 29	E	Green plates	$C_{23}H_{27}N_4I$	I,	26·1	26·1
7-Ethyl-3,3-dimethyl-3*H*-1,7-diazaindene-2 [d]	Et	245—246	60; 33	E(30)	Bronze needles	$C_{25}H_{31}O_4N_4Cl$ [c]	Cl,	7·0	7·3
3-Methyl-2-benzoxazole	Me	268—269	44; 26	GM	Blue needles	$C_{21}H_{22}ON_2I,H_2O$ [e]	I,	26·4	26·6
3-Ethyl-2-benzoxazole	Et	252—253	94; 52	E	Purple	$C_{23}H_{26}ON_2I,HI$	I,	40·7	41·25
3-Methyl-2-benzothiazole	Me	269—270 [b]	73; 52	M	Indigo needles	$C_{21}H_{22}N_2IS$	I,	26·6	26·7
3-Methylnaphtho(1′,2′:4,5)thiazole-2	Me	236—237	23; 8	G(170)	Green	$C_{25}H_{24}N_2IS,H_2O$	I,	23·3	23·35

[a, b] See Table 4. [c] Perchlorate. [d] $\lambda_{max.}$ 6090 Å (log ε 5·30). [e] Bromide, purple needles, m. p. 262° (Found: Br, 18·4. $C_{21}H_{22}ON_2Br,H_2O$ requires Br 18·6%).

$C_{20}H_{24}N_3I$ requires I, 29·3%). The three following dyes were obtained similarly. **3,3-*Dimethyl*-2-p-*dimethylaminostyryl*-3H-1,7-*diazaindene* 7-*methiodide*** (38; 23%), bronze-green needles, m. p. 272—273° (decomp.), from methanol (1 in 20) (Found: C, 52·8; H, 5·9; I, 27·9. $C_{20}H_{24}N_3I,H_2O$ requires C, 53·2; H, 5·8; I, 28·1%). **(1,3,3-*Trimethyl*-3H-1,7-*diazaindene*-2)-(2,5-*dimethyl*-1-*phenyl*-3-*pyrrole*)*dimethincyanine perchlorate*** (53; 29%), orange needles with a steely reflex, m. p. 282° (decomp.), from methanol (1 in 60) (Found: N, 9·2. $C_{24}H_{26}O_4N_3Cl$ requires N, 9·2%). **(3,3,7-*Trimethyl*-3H-1,7-*diazaindene*-2)(2,5-*dimethyl*-1-*phenyl*-3-*pyrrole*)*dimethincyanine perchlorate*** (49; 12%), red prisms with a blue reflex, m. p. 259—260° (decomp.), from ethanol (1 in 55) (Found: N, 9·05. $C_{24}H_{26}O_4N_3Cl$ requires N, 9·2%). The last two dyes were prepared from 2,5-dimethyl-1-phenylpyrrole-3-aldehyde (cf. Brooker and Sprague [17]).

(c) *Merocyanines.* A solution of the diazaindene 1-methiodide (0·34 g.) and 5-ethoxymethylene-3-ethyl-2-thiothiazolid-4-one (ethoxymethylene-*N*-ethylrhodanic acid) (0·40 g.) in ethanol (5·0 ml.) was refluxed with one drop of piperidine for 1 hr. The solid (0·29 g.) which separated on cooling recrystallised from ethanol (35 ml.) to give **5-(1,2-*dihydro*-1,3,3-*trimethyl*-3H-1,7-*diazainden*-2-*ylidene*)*ethylidene*-3-*ethyl*-2-*thiothiazolid*-4-*one*** (0·26 g.) as red needles and plates with a blue reflex, m. p. 223° (Found: S, 18·6. $C_{17}H_{19}ON_3S_2$ requires S, 18·6%), $\lambda_{max.}$ 4830 Å (log ε 4·84). Similarly prepared was **5-(2,7-*dihydro*-3,3,7-*trimethyl*-3H-1,7-*diazainden*-2-*ylidene*)*ethylidene*-3-*ethyl*-2-*thiothiazolid*-4-*one*** (69; 58%), red plates with a blue reflex, m. p. 257—259° (from 2-methoxyethanol–methanol) (Found: S, 18·9. $C_{17}H_{19}ON_3S_2$ requires S, 18·6%), $\lambda_{max.}$ 5430 Å (log ε 4·83).

A solution of the diazaindene 1-methiodide (0·54 g.) and 3-methyl-1-phenylpyrazol-5-one (0·31 g.) in pyridine (3·0 ml.) was refluxed with ethyl orthoformate (1·0 ml.) for 45 min. The solid obtained by pouring the solution into water was chromatographed in chloroform on activated alumina. The main orange band was eluted and the eluate evaporated to yield a solid (0·37 g.) which gave **4-(1,2-*dihydro*-1,3,3-*trimethyl*-3H-1,7-*diazainden*-2-*ylidene*)*ethylidene*-3-*methyl*-1-*phenylpyrazol*-5-*one*** (0·29 g.) as red rhombs, m. p. 187—188°, by crystallisation from ethanol (12 ml.) (Found: C, 73·4; H, 6·3. $C_{22}H_{22}ON_4$ requires C, 73·7; H, 6·2%), $\lambda_{max.}$ 4600 Å (log ε 4·68). Similarly prepared was **4-(2,7-*dihydro*-3,3,7-*trimethyl*-3H-1,7-*diazainden*-2-*ylidene*)-*ethylidene*-3-*methyl*-1-*phenylpyrazol*-5-*one***, obtained as red needles, m. p. 251—252°, by crystallisation from ethanol (Found: C, 73·2; H, 6·0. $C_{22}H_{22}ON_4$ requires C, 73·7; H, 6·2%), $\lambda_{max.}$ 5220 Å (log ε 4·89).

(d) *Dye* (XXIV). Diazaindene 7-methiodide (3·02 g.) was refluxed for 30 min. with acetic anhydride (10 ml.) containing ethyl trithio-orthoformate (2·2 ml.). The solvent was distilled off under reduced pressure and the residue was triturated with acetone to leave a sticky brown solid (1·78 g.). This crude ethylthiovinyl quaternary salt (0·84 g.) was refluxed for 45 min. with diazaindene 1-methiodide (0·75 g.) in ethanol (5·0 ml.) containing triethylamine (0·5 ml.). The solid (0·47 g.) which separated on cooling was recrystallised from ethanol (10 ml.) to give **(1,3,3-*trimethyl*-3H-1,7-*diazaindene*-2)(3,3,7-*trimethyl*-3H-1,7-*diazaindene*-2)*trimethincyanine iodide*** (0·33 g.) as lustrous blue prisms, m. p. 261—262° (decomp.) (Found: I, 25·8. $C_{23}H_{27}N_4I$ requires I, 26·1%).

Dye Preparation with the Crude Methiodide.—Diazaindene (VI) (160 mg., 0·01 mole) was refluxed for 1 hr. with dry methyl iodide (1·0 ml.). The residue remaining after distillation of the excess of methyl iodide was refluxed for 2 hr. with *p*-dimethylaminobenzaldehyde (0·30 g.) in ethanol (5·0 ml.) containing one drop of piperidine. After neutralisation with a little acetic acid, the solution was evaporated to dryness under reduced pressure, and the residue was chromatographed in chloroform on activated alumina. The first band (purple) was eluted and the eluate evaporated to dryness. A solution of the product in methanol (100 ml.; 2·5 ml. of solution diluted to 100 ml.) showed the absorption spectrum of the dye from the 1-methiodide, and had $E_{max.}$ 1·06 corresponding to a yield of 6·2%. The second band (red) similarly treated gave a solution in methanol (100 ml.; 0·5 ml. diluted to 100 ml.) which had the spectrum of the 7-methyl dye ($E_{max.}$ 1·66; yield 55%).

Dye Preparation from Compound (VII).—The high-boiling fraction (8·6 g.) from the previously described preparation of diazaindene (VI) was refluxed in acetone with methyl iodide (5·0 ml.) for 2 hr. Evaporation of the solution left a brown deliquescent powder (12·9 g.), from which no pure material could be isolated. This material (1·5 g.) and 3-methyl-2-methylthiobenzothiazolium toluene-*p*-sulphonate (1·8 g.) were refluxed for 2 hr. in ethanol (30 ml.) containing triethylamine (1·0 ml.). The solution was poured into aqueous potassium iodide, and the dyes were extracted with chloroform. The extracts were dried (Na_2SO_4) and evaporated to dryness, and

the product was chromatographed in chloroform on activated alumina. The first, yellow band was eluted and the dye identified spectroscopically as the methincyanine (XIV; $n = 0$). Subsequently a purple band was eluted, the eluate was evaporated to dryness, and a solution of the product in ethanol was treated with an aqueous solution of sodium perchlorate. The precipitated solid (0·16 g.), m. p. 197—199°, recrystallised from ethanol to yield (*3,3,7-trimethyl-*3H-*1,7-diazaindene-2*)(*3-methyl-2-benzothiazole*)-β-*isopropyltrimethincyanine perchlorate* (XIV; $n = 1$, R = Pr^i) as green crystals, m. p. 217—218°, undepressed by a sample prepared by the method described below (Found: N, 8·6; Cl, 7·2; S, 6·9. $C_{24}H_{25}O_4N_3ClS$ requires N, 8·6; Cl, 7·2; S, 6·5%), $\lambda_{max.}$ 5740 Å (log ε 5·14).

2-*Isobutyrylmethylene-3-methylbenzothiazoline*.—Isobutyryl chloride (12·5 ml.) was added dropwise, with stirring to a solution/suspension of 2,3-dimethylbenzothiazolium toluene-*p*-sulphonate (33·5 g.) in dry pyridine (100 ml.), the temperature being kept below 0°. Then stirring was continued for successive 30-minute periods at 0°, room temperature, and 100°. The solvent was distilled off under reduced pressure and the residue was added to ice and water. The precipitated solid was washed with cold water, dried, and extracted (Soxhlet) with light petroleum (b. p. 60—80°). The extracts deposited a solid (17·0 g.), m. p. 120—124°, which yielded the *benzothiazoline* as cream-coloured plates, m. p. 131—132°, by crystallisation from dilute ethanol (Found: C, 67·1; H, 6·6; S, 13·2. $C_{13}H_{15}ONS$ requires C, 66·9; H, 6·5; S, 13·7%).

2-(*2-Ethylthio-3-methylbut-1-enyl*)-*3-methylbenzothiazolium Iodide* (XV).—The benzothiazoline was dissolved in methanol (150 ml.) containing ethanethiol (7·5 ml.). The solution, cooled in ice–salt, was saturated with dry hydrogen chloride. A solid separated but subsequently dissolved. The solution, after 16 hr. at room temperature, was treated with a saturated solution of potassium iodide (35 g.) in water, then diluted with water. The solid which separated (7·0 g.) was washed with water and recrystallised from ethanol to yield the *benzothiazolium iodide* as yellow needles, m. p. 150—151° (Found: I, 31·55; S, 15·4. $C_{15}H_{20}NIS_2$ requires I, 31·3; S, 15·8%).

Preparation of Dye from (XV).—A solution of the benzothiazolium iodide (1·01 g.) and 2,3,3-trimethyl-3*H*-1,7-diazaindene 7-methiodide (0·76 g.) in ethanol (10 ml.) was refluxed for 2 hr. with triethylamine, and the solution poured into aqueous sodium perchlorate solution. The dried precipitate was chromatographed to yield the trimethin-cyanine (XIV; $n = 1$, R = Pr^i), m. p. 219—220°, by crystallisation from ethanol. Its light absorption (visible and infrared) was identical with that of the dye prepared from (VII).

Symmetrical Trimethincyanines.—The symmetrical trimethincyanines were prepared by refluxing the appropriate methyl heterocyclic quaternary salt with ethyl orthoformate in pyridine, according to the method of Hamer.[24] *Bis-*(*1,3,3-trimethyl-*3H-*indole-2*)*trimethincyanine perchlorate*, from 1,2,3,3-tetramethyl-3*H*-indolium iodide followed by treatment with aqueous sodium perchlorate solution, formed red plates with a blue reflex, m. p. 264°, by crystallisation from methanol (Found: N, 6·3. $C_{25}H_{29}O_4N_2Cl$ requires N, 6·1%). *Bis-*[*3-methylnaphtho*(1′,2′ : 4,5)*thiazole-2*]*trimethincyanine toluene-*p*-sulphonate* formed bronze needles, m. p. 269—270° (decomp.) (from ethanol) (Found: S, 15·4. $C_{34}H_{28}O_3N_2S_3$ requires S, 15·8%).

The light-absorption measurements were made in ethanolic solution on a Unicam S.P. 500 spectrophotometer.

We thank the directors of Ilford Limited for permission to publish this paper, Mr. V. W. Dolden for assistance with the preparative work, Miss J. Connor, Miss J. A. Logan and Mrs. S. E. Bliss for the microanalytical results, and Mr. L. R. Brooker for the light-absorption data.

ILFORD LIMITED, RENWICK LABORATORY,
ILFORD, ESSEX.

[*Received, March 24th*, 1959.]

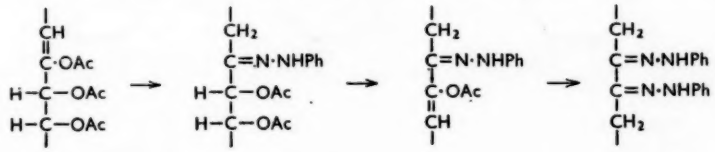
[24] Hamer, *J.*, 1929, 2598.

651. *The Reaction of Phenyl- and 2,4-Dinitrophenyl-hydrazine with Some Unsaturated Glucose Derivatives.*

By W. M. Corbett.

The products of reaction of tetra-*O*-acetyl-2-hydroxy-D-glucal, 2-hydroxy-D-glucal, kojic acid, and 2-methoxy-2,3-D-glucal * with phenyl- and 2,4-dinitrophenyl-hydrazine have been examined. The hydrolysis of phenylosazones and alkaline rearrangement of the resulting osones has been described.

The reaction of phenylhydrazine with 2-hydroxy-D-glucal and its acetate has been examined by Bergmann and Zervas.[1] Although the tetra-acetate (I) does not possess a carbonyl group, it reacts readily with phenylhydrazine, giving a phenylosazone whose structure has been shown to be (II). The initial reaction must be attack of the reagent on the 2-acetyl group which is activated by the double bond (cf. Evans's postulation [2] of the occurrence of a similar reaction in alkaline solutions of sugars). It is postulated that this is then followed by a second reaction involving the elimination of the 4-acetyl group, the resulting unsaturated derivative reacting with further reagent to give an osazone.



2-Hydroxyglucal (V) itself reacts with phenylhydrazine in a different way. At room temperature,[1] the product isolated has the structure (VI). The acetyl-free starting material will exist as a mixture of the enol and the carbonyl form, the latter reacting with phenylhydrazine in the normal way to give the osazone. It has now been observed that after reaction at higher temperature, the product has a higher melting point: it is also obtained when Bergmann and Zervas's osazone (VI) is heated with phenylhydrazine and acetic acid. Analysis shows that the osazone undergoes elimination of water at elevated temperatures.

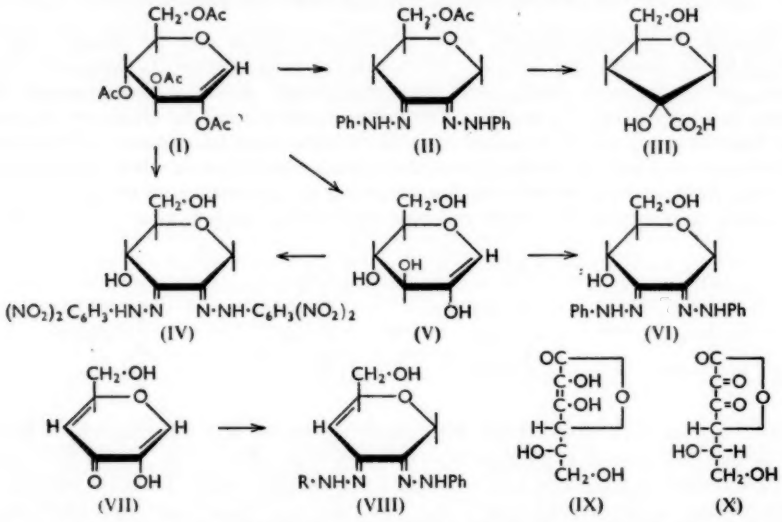
It is well established that water is eliminated when phenylosazones are treated with dilute acid, but the structures of the products have still to be conclusively established. It has been suggested that an anhydro-ring is formed by elimination of water from two hydroxyl groups of the sugar moiety [3] or from a hydroxyl group of the sugar moiety and the amine group of the phenylhydrazine residue.[4] Formation of a cyclic anhydride by either process is unlikely in this particular case because our products are pyranoses, so it is more reasonable that the elimination should be from the sugar unit, yielding an unsaturated derivative. This would lead to an isomer of the phenylosazone (VIII; R = Ph) expected from kojic acid (VII). This derivative (VIII; R = Ph) has been prepared, and shown to differ from the compound prepared from 2-hydroxyglucal. It may be that the relation between the two phenylosazones is similar to that between the similar derivatives of ascorbic acid (IX) and dehydroascorbic acid (X).[5] The reaction of kojic acid with phenyl- and 2,4-dinitrophenyl-hydrazine appears to be normal in that the expected derivatives (VIII) are produced, and, unlike the situation with 2-hydroxyglucal, the

* 2,3- denotes the position of the double bond.

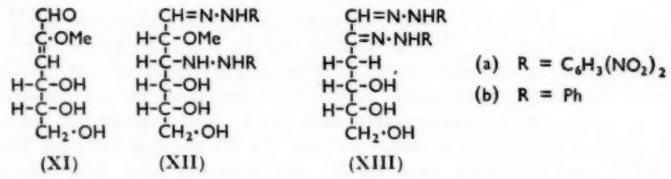
[1] Bergmann and Zervas, *Ber.*, 1931, **64**, 1434.
[2] Evans, *Chem. Rev.*, 1942, **31**, 537.
[3] Hardegger and Schreier, *Helv. Chim. Acta*, 1952, **35**, 232, 993; Schreier, Stöhr, and Hardegger, *ibid.*, 1954, **37**, 35, 574; Mester and Major, *J. Amer. Chem. Soc.*, 1955, **77**, 4305.
[4] Percival, *J.*, 1945, 783.
[5] Herbert, Hirst, Percival, Reynolds, and Smith, *J.*, 1933, 1270.

same product is obtained with phenylhydrazine at room temperature and elevated temperatures.

2-Hydroxyglucal tetra-acetate appears not to react with 2,4-dinitrophenylhydrazine in acetic acid or alcohol, possibly owing to the lower reactivity of 2,4-dinitrophenylhydrazine. A solution of the dinitrophenylhydrazine in hydrochloric acid, however, does react with the tetra-acetate. The same product is produced by reaction with 2-hydroxyglucal itself, and analyses indicate structure (IV). Clearly the initial reaction of the reagent with the tetra-acetate is hydrolysis of the acetyl groups.



Kenner and Richards [6] isolated 2-methoxy-2,3-D-glucal * (XI) which with 2,4-dinitrophenylhydrazine gave an osazone whose structure was given as (XIIa). The formation of of such a derivative is contrary to the above findings from which structure (XIIIa) would be predicted. Re-investigation of the osazone has revealed the absence of a methoxyl group.[7] The analyses quoted by Kenner and Richards for the dinitrophenylhydrazine derivative and its triacetate are in close agreement with those calculated for (XIIIa) and its acetate, although the melting point of the osazone is considerably higher than that given for the osazone of 3-deoxy-D-mannose.[8] To provide further evidence for structure (XIII), the phenylhydrazine derivative has been prepared; this too was free from methoxyl groups, and analyses indicated structure (XIIIb).



If the phenylhydrazine derivative is indeed (XIII*b*), it should on mild acid hydrolysis followed by treatment with alkali give α- and β-*meta*saccharinic acid. Because the

* See footnote, p. 3213.

[6] Kenner and Richards, *J.*, 1956, 2921.
[7] Machell and Richards, personal communication.
[8] Foster, Overend, Stacey, and Vaughan, *J.*, 1953, 3308.

alkaline rearrangement of osones is new, the reactions of glucose phenylosazone and the phenylhydrazine derivative of 2-hydroxyglucal acetate (II) were first examined. Since only small amounts of material were available, the acidic products could be identified only by paper chromatography. Acid-hydrolysis of glucose phenylosazone gave glucosone and a new compound which is probably one of the two possible forms of glucosone monophenylhydrazone, as well as (*a*) a lactone which corresponded to D-mannolactone and (*b*) small amounts of D-gluconolactone. The concentrations of the two lactones increased when the crude material was treated with lime-water. The rearrangement of the osone to acids in acidic solutions is in agreement with Theander's findings.[9] Limited asymmetric synthesis appears to be a feature of the benzilic acid rearrangement of some αβ-dicarbonyl compounds into acids, *e.g.*, the saccharinic acids, of which one form usually predominates. The phenylhydrazine derivative of 2-hydroxyglucal acetate produced an acid which, as expected, was chromatographically identical with the acid of postulated structure (III) produced by the alkaline degradation of hepta-*O*-acetyl-2-hydroxylcellobial.[10] When the phenylhydrazine derivative of 2-methoxy-2,3-D-glucal was similarly treated, a mixture of lactones was isolated which behaved identically with α- and β-*glucometa*saccharolactone. It is evident that the 2,4-dinitrophenylosazone obtained by Kenner and Richards has the structure (XIIIa).

Experimental

Reaction of 2-Hydroxyglucal Tetra-acetate with 2,4-Dinitrophenylhydrazine.—2-Hydroxyglucal tetra-acetate (1·0 g.) was dissolved in ethanol (10 ml.) and the solution was diluted with water (240 ml.), treated with a saturated solution (500 ml.) of 2,4-dinitrophenylhydrazine in 2N-hydrochloric acid, and kept at room temperature for 18 hr. before the bright red precipitate was filtered off and washed with water until free from acid. The product, 1,2,3-*trideoxy*-2,3-*bis*-(2,4-*dinitrophenylhydrazono*)-D-*glucopyranose* (IV) (0·8 g.), had m. p. 186—190°, raised to 234·5—236° by several recrystallisations from acetone—ethanol (Found: C, 41·5; H, 3·4. $C_{18}H_{16}O_{11}N_8$ requires C, 41·5; H, 3·1%).

Reactions of 2-Hydroxyglucal.—(a) *With phenylhydrazine.* 2-Hydroxyglucal (0·80 g.), prepared by a Zemplén deacetylation of the tetra-acetate, was dissolved in 30% acetic acid (10 ml.), and to it was added phenylhydrazine (2 ml.) in 30% acetic acid (4 ml.). The mixture was heated at 95° for ¾ hr., and to the cooled solution was added water. The crystals which gradually separated were digested with cold ethanol, then recrystallised twice from ethanol–acetone to give a 1,2,3-*trideoxy*-2,3-*bisphenylhydrazono*-4,5(?)-D-*glucal* * (VI), m. p. 240—241° (Found: C, 67·2; H, 5·6. $C_{18}H_{18}O_2N_4$ requires C, 67·2; H, 5·6%).

Reaction at room temperature gave Bergmann and Zervas's osazone.[1] This (50 mg.) was heated at 90° for 1 hr. with 30% acetic acid (2·5 ml.) and phenylhydrazine (0·5 ml.). On addition of water crystals separated which were digested with ethanol to give an osazone, m. p. 230—235°, undepressed on admixture with that obtained at 95°.

(b) *With 2,4-dinitrophenylhydrazine.* 2-Hydroxyglucal (1·4 g.) was dissolved in a saturated solution (1 l.) of 2,4-dinitrophenylhydrazine in 2N-hydrochloric acid. After several days at room temperature, the red precipitate was centrifuged off, washed with water until free from acid, dried, and extracted with chloroform. Concentration of the extract gave a residue which crystallised from ethanol–acetone to give an osazone (0·2 g.) having m. p. 230—232°, undepressed on admixture with that obtained from the tetra-acetate (Found: C, 41·9, H, 3·1%).

Reaction of Kojic Acid.—(a) *With phenylhydrazine.* Kojic acid (1 g.) was treated in hot water (20 ml.) with phenylhydrazine (1 ml.) in acetic acid (2 ml.), heated at 90° for 1 hr., and then cooled. The dark red syrup which separated was dissolved in a little ethanol and allowed to crystallise. The dark red crystals were filtered off and washed with a little ethanol, to give yellow crystals (0·6 g.). After three recrystallisations from aqueous ethanol, the *phenylosazone* (VIII; R = Ph) had m. p. 169·5—171° (Found: C, 67·3; H, 5·5. $C_{18}H_{18}O_2N_4$ requires C, 67·2; H, 5·6%). Reaction at room temperature gave the same product, m. p. 171—172°.

(b) *With 2,4-dinitrophenylhydrazine.* To 2,4-dinitrophenyhydrazine (1·3 g.) in warm

* See footnote, p. 3213.

[9] Theander, *Acta Chem. Scand.*, 1958, **12**, 1897.

[10] Corbett and Kidd, *J.*, 1959, 1594.

XUM

2N-hydrochloric acid (100 ml.), kojic acid (0·5 g.) was added. The mixture was heated at 70° for 3 hr. during which considerable degradation occurred. The precipitate was crystallised twice from anisole–light petroleum (b. p. 40—60°), to give a *2,4-dinitrophenylosazone* (0·1 g.), m. p. 221—224° (Found: C, 43·4; H, 3·1. $C_{18}H_{14}O_{10}N_8$ requires C, 43·0; H, 2·8%).

Reactions of 2-Methoxy-2,3-D-glucal.—(a) *With 2,4-dinitrophenylhydrazine.* 2-Methoxy-2,3-D-glucal was prepared and treated with 2,4-dinitrophenylhydrazine as described by Kenner and Richards.[9] The osazone had m. p. 263—264° (Kenner and Richards give m. p. 266—268°, and Foster *et al.*[8] give m. p. 205°, for 3-deoxy-D-mannose 2,4-dinitrophenylosazone) (Found: C, 41·4; H, 3·7; OMe, 0·0. Calc. for $C_{18}H_{18}O_{11}N_8$: C, 41·4; H, 3·5%).

(b) *With phenylhydrazine.* To crude 2-methoxy-2,3-D-glucal (1·28 g.) in water (45 ml.), phenylhydrazine (3 ml.) and acetic acid (3 ml.) were added. After 4 days at room temperature, the precipitate (0·66 g.) was filtered off and digested with ether, to give yellow *3-deoxy-D-glucosazone* (0·25 g.), m. p. 139—140°, depressed on admixture with 5-hydroxymethyl furfuraldehyde phenylhydrazone (Found: C, 62·9; H, 6·4; OMe, 0·0. $C_{18}H_{22}O_3N_4$ requires C, 63·3; H, 6·5%).

Hydrolysis of Phenylosazones.—(a) *Glucose phenylosazone.* Glucose phenylosazone (1·0 g.) was suspended in chloroform (115 ml.), and concentrated hydrochloric acid (18·4 ml.) in water (83 ml.) was added. The mixture was refluxed for ½ hr., then the aqueous layer was washed with chloroform and shaken with *N*-methyldioctylamine [11] (50 ml.) in chloroform (1 l.) until neutral. Addition of 2,4-dinitrophenylhydrazine in hydrochloric acid to a portion of the aqueous solution gave immediately a precipitate which after being washed and dried had m. p. 250—251° (decomp.), undepressed on admixture with glucosazone. The aqueous solution was treated with charcoal and concentrated under reduced pressure to a solid (0·339 g.). The material crystallised partly on trituration with alcohol. After several recrystallisations from ethanol–ether, the very fine, pale yellow needles had m. p. 169—170° (decomp.), depressed on admixture with glucose phenylhydrazone, m. p. 149—150°. They were soluble in water and reduced Fehling's solution in the cold. They were probably one of the two possible forms of *glucosone monophenylhydrazone* (Found: C, 53·6; H, 6·0; N, 10·3. $C_{12}H_{16}O_5N_2$ requires C, 53·8; H, 6·0; N, 10·4%).

The ethanol liquors from the trituration were concentrated to a straw-coloured syrup which reduced cold Fehling's solution, decolorised permanganate, and reacted readily with 2,4-dinitrophenylhydrazine. Chromatography of the acidic syrup in ethyl acetate–acetic acid–water (10 : 1·3 : 1) and in butan-1-ol–pyridine–water (6 : 4 : 3) gave two lactones, detected by permanganate–periodate [12] and hydroxylamine–ferric chloride sprays.[13] The main lactone behaved identically with mannonolactone, and on admixture no separation was observed. The minor component behaved similarly to gluconolactone. The concentrations of these lactones were increased by treatment of the hydrolysis product with calcium hydroxide.

(b) *Phenylosazone of tetra-O-acetyl-2-hydroxyglucal.* The osazone was deacetylated catalytically with sodium methoxide, to give the unsubstituted osazone, m. p. 178—179° (Bergmann and Zervas [1] give m. p. 183°) (Found: C, 66·7; H, 6·2; N, 16·8. Calc. for $C_{18}H_{22}O_3N_4$: C, 66·6; H, 6·2; N, 17·3%). This osazone (85 mg.) was treated as above, and the resultant product on chromatographing gave a main component (R_{Lactic} 0·45) which was acidic, reacted slowly with periodate, and did not form a lactone. It appeared to be identical with the acid produced by the alkaline degradation of 2-hydroxycellobial acetate.

(c) *Phenylosazone from 2-methoxy-2,3-D-glucal.* The phenylosazone (*ca.* 50 mg.) was treated as above except that dioxan was used instead of chloroform. Chromatography of the resulting syrup revealed the presence of two lactones of R_{Lactic} 0·47 and 0·56 which behaved similarly to α- and β-*glucometa*saccharolactones. An acid with R_{Lactic} 0·75 was also detected.

The author is indebted to Mr. A. T. Masters for the microanalyses. This work forms part of the fundamental research programme of the British Rayon Research Association.

British Rayon Research Association, Heald Green Laboratories,
Wythenshawe, Manchester, 22. [*Received, March 25th*, 1959.]

[11] Smith and Page, *J. Soc. Chem. Ind.*, 1948, **67**, 48.
[12] Lemieux and Bauer, *Analyt. Chem.*, 1954, **26**, 920.
[13] Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5859.

652. *The Oxidation of Derivatives of o-Phenylenediamine. Part VII.*[1] *Bromination of Anilinoaposafranines and Related Compounds.*

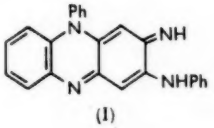
By VINCENT C. BARRY, J. G. BELTON, J. F. O'SULLIVAN, and DERMOT TWOMEY.

It has been established that anilinoaposafranine, on bromination in chloroform and subsequent treatment with alkali, yields a tetrabromo-derivative. No bromine enters the phenazine nucleus. Arguments are advanced which prove that bromine has replaced the hydrogen of the 2- and 3-imino-groups atached to the phenazine nucleus, and that the third and fourth bromine atoms have substituted the *ortho*- and the *para*-position of the N^3-phenyl group. The isomer of anilinoaposafranine yields the dibromo-derivative, 2-bromoamino-3-*p*-bromophenylimino-3,5-dihydro-5-phenylphenazine.

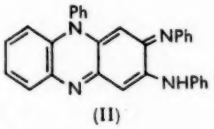
Aposafranone forms a monobromo-derivative, the bromine entering the 2-position *ortho* to the carbonyl group. With anilinoaposafranone four bromine atoms again enter the molecule, one replacing the imino-hydrogen atom, and the remaining three the 2-, 4-, and 6-hydrogen atoms of the anilino-group.

The structures of a number of other brominated derivatives of anilinoaposafranine have been elucidated.

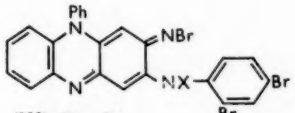
IN Part I [2] treatment of anilinoaposafranine (I) and its isomer (XVIII) was described as leading to tribromo- and dibromo-derivatives respectively. The bromine was thought to have entered the *ortho*-positions of the quinonoid system, and to have replaced the hydrogen of the =NH group in anilinoaposafranine. As indicated in Part V,[3] a continuing investigation of the bromination studies has shown the situation to be complex, and it is now clear that the formulations of the bromo-derivatives in Part I are incorrect. When bromination of the compounds is carried out under our conditions, no bromine enters the phenazine nucleus.



(I)



(II)



(III) X = Br
(IV) X = H

When derivatives of anilinoaposafranine are treated in chloroform with excess of bromine, an unexpectedly large proportion of bromine is taken up (*ca.* 7 bromine atoms per mole). Treatment of the brominated products in ethanol with ammonia or alkali results in a loss of some bromine, and we are concerned in this paper with the structure of the alkali-stable brominated compounds.

Addition of a large excess of bromine (12 mols.) to anilinoaposafranine (I) gave a product which, on treatment in ethanol with ammonia, gave a tetrabromo-derivative (III). In the bromination of anilinoaposafranine (I), described in Part I,[2] carbon tetrachloride was used as solvent and a tribromo-derivative resulted. The use of chloroform as solvent enabled a fourth bromine atom to substitute the molecule. Unless a large excess of bromine is employed the product will contain some di- and tri-brominated compounds which are difficult to eliminate by column chromatography. The tetrabromo-derivative (III), on being heated under reflux with aniline, was converted into the bromine-free rimino-compound (II).[3] The four bromine atoms, therefore, in compound (III) must be present in the groups substituting the 2- and the 3-position of the phenazine nucleus.

[1] Part VI, Barry, Belton, O'Sullivan, and Twomey, *J.*, 1958, 4495.
[2] *Idem*, *J.*, 1956, 888.
[3] *Idem*, *J.*, 1958, 859.

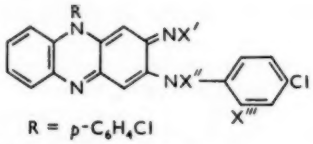
XUM

The tribromoanilinoaposafranine described in Part I [2] was thought to be the 1,4,N^3-tribromo-compound which on degradation in a sealed tube with ethanolic sulphuric acid yielded a bromine-free hydroxy-derivative. The analytical data for this compound fitted a 1,4-dihydroxyanilinoaposafranone, and the failure to introduce more than one acetyl group into it was attributed to hydrogen-bonding. It is now clear that the degradation product was hydroxyaposafranone which also results from anilinoaposafranine itself under the same degradative conditions. The reinterpretation of these facts affords further evidence that no bromination occurs in the phenazine nucleus.

The tetrabromoanilinoaposafranine (III), when heated under reflux with cyclohexylamine, gave a mixture from which a tribromoanilinoaposafranine (IV) was isolated by chromatography on alumina. One of the four bromine atoms is thus somewhat labile although stable to alkali, and for reasons which will be made clear during the discussion we have assigned this bromine to the –NH– group of the 2-anilino-substituent in the phenazine nucleus.

As already shown,[3] anilinoaposafranines may be converted into rimino-compounds by heating them with the appropriate alkyl- or cycloalkyl-amines, the =NH group being replaced by alkyl- or cycloalkyl-imino-groupings. However, in the conversion of the tetrabromoanilinoaposafranine (III) into the tribromo-derivative (IV), a rimino-compound was not formed, and we attribute this failure to the fact that =NH has been converted by bromination into =NBr which, although replaceable by boiling aniline, is stable to boiling cyclohexylamine. Further evidence will be given below in favour of our contention that a second bromine atom is present as =NBr in the tetrabromo-compound (III).

The third and the fourth bromine atom are in the *ortho*- and the *para*-position of the anilino-group substituting position 2 of the phenazine nucleus. This deduction is based on the following facts:

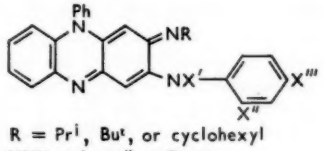


R = *p*-C_6H_4Cl

(V) X′=X″ = X‴ = H

(VI) X′=X″ = X‴ = Br

(VII) X′=X‴ = Br ; X″= H

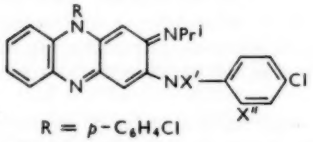


R = Pr^i, Bu^t, or cyclohexyl

(VIII) X′ = X″=X‴ = H

(IX) X′ = X″=X‴ = Br

(IXa) X′=H ; X″=X‴=Br ; R = cyclohexyl

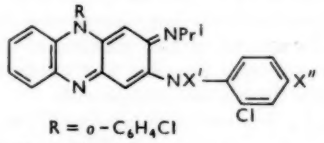


R = *p*-C_6H_4Cl

(X) X′=X″= H

(XII) X′=X″= Br

(XIV) X′=H ; X″=Br



R = *o*-C_6H_4Cl

(XI) X′ = X″= H

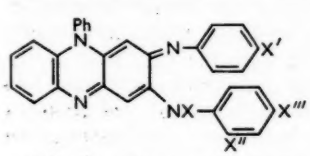
(XIII) X′ = X″= Br

(XV) X′= H, X″= Br

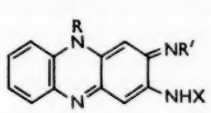
The rimino-compounds (VIII), in which the hydrogen of the =NH group has been replaced by alkyl or cycloalkyl gave tribromo-derivatives (IX), in contrast to the tetrabromo-derivative (III), obtained from anilinoaposafranine. The tribromo-derivative (IX; R = cyclohexyl) lost one bromine atom in boiling cyclohexylamine, to yield the dibromo-derivative (IXa). Again the dichlorinated rimino-compounds (X and XI) yielded only dibromo-derivatives (XII and XIII), respectively, and these are converted by boiling cyclohexylamine into the monobromo-derivatives (XIV and XV). Further, the

dichloro-anilinoaposafranine (V) on bromination gave a tribromo-compound (VI), which was converted by boiling cyclohexylamine into the dibromo-dichloro-anilinoaposafranine (VII), with the elimination of a bromine atom. It is clear therefore that the failure to introduce more than two bromine atoms into compounds (XI and X) is due to the fact that the *ortho*- and the *para*-position respectively of the anilino-group are already occupied by chlorine. A repetition of the degradation experiment with the tetrabromo-compound (III) yielded, as before, the bromine-free hydroxyaposafranone, but on this occasion it proved possible to isolate also a small amount of the dibromo-compound (XXIX). This is a further confirmation that two bromine atoms are present in the 2,4-positions of the N^2-phenyl group, and that no bromine has entered the phenazine nucleus.

We have now indicated the positions occupied by the four bromine atoms in tetrabromo-anilinoaposafranine (III), and in the various rimino-compounds (IX, XII, XIII). The

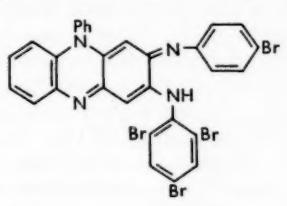


(XVI) X = X″ = H; X′ = X‴ = Br
(XVII) X = X′ = X″ = X‴ = Br

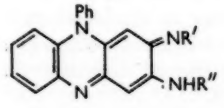


	R	R′	X
(XVIII)	Ph	Ph	H
(XIX)	*p*-C	*p*-C	H
(XX)	ch	ch	H
(XXI)	*p*-C	*p*-C	Br
(XXII)	ch	ch	Br
(XXIII)	Ph	*p*-Br	Br

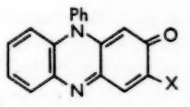
p-C = *p*-C_6H_4Cl
p-Br = *p*-C_6H_4Br
ch = cyclohexyl



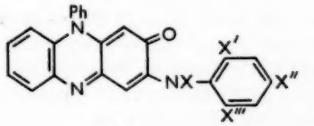
(XXIV)



(XXV) R′ = R″ = cyclohexyl
(XXVI) R′ = cyclohexyl; R″ = Br



(XXVII) X = Br
(XXVIII) X = NHPh



	X	X′	X″	X‴
(XXIX)	H	H	Br	Br
(XXX)	H	Br	Br	Br
(XXXI)	Br	Br	Br	Br

phenyl rimino-compound (II), however, unlike the alkyl or cycloalkyl compounds of this class, formed a tetrabromo-derivative, and the evidence here favours the placing of the fourth bromine atom in the *para*-position of the =NPh group in position 3 of the phenazine nucleus. This evidence is provided by synthesis of the dibromo-compound (XVI), by condensation of *o*-aminodiphenylamine and 4,5-di-*p*-bromoanilino-*o*-quinone, which on further bromination yielded the identical tetrabromo-derivative (XVII), already obtained from compound (II), by direct bromination. Supporting evidence is afforded by the behaviour on bromination of the isomers of the anilinoaposafranines. Thus the isomer (XVIII) gave under the usual conditions a dibromo-derivative which is stable to boiling cyclohexylamine. With aniline under reflux it gave the bromine-free phenyl rimino-compound (II), showing that again with this group of compounds only the 2- and 3-substituents of the phenazine nucleus are concerned in the bromination. Compound

(XVIII) has already been shown[1] to form a monoacetyl derivative. The dibromo-derivative, however, could not be acetylated. It is presumed, therefore, that one of the bromine atoms has substituted in the NH_2– group and, by analogy from compound (XVII), the second bromine atom must be placed in the *para*-position of the =NPh residue. This is confirmed by the results obtained from bromination of compounds (XIX) and (XX), both of which yielded monobromo-derivatives (XXI and XXII). The fact that the dibromo-derivative (XXIII), on degradation with ethanolic sulphuric acid in a sealed tube, gave a bromine-free product (cf. Part I[2]) which we now know to be hydroxyaposafranone, is readily understood on the basis of the structure here advanced for compound (XXIII).

The bromine linked to nitrogen in the 2-arylamino-substituent of the phenazine nucleus is remarkably stable, resisting alcoholic potassium hydroxide and boiling dilute acetic acid. It is labile in boiling cyclohexylamine, in part being eliminated from the molecule and in part, we suspect, being transferred to the 6-position of the already brominated phenyl nucleus. Thus in one experiment it was possible to separate chromatographically a second tetrabromo-compound from the product resulting from the treatment of the tetrabromo-derivative (XVII) with cyclohexylamine. This tetrabromo-compound was much paler, had a sharp melting point and altered colour reactions in acid, and probably has the structure (XXIV). In many other experiments, boiling with cyclohexylamine gave mixtures of bromo-compounds which it was impossible to separate chromatographically. The bromination of compound (XXV) gave an interesting result, one bromine atom entering the molecule with the simultaneous displacement of a cyclohexyl group. As it has already been shown that the =N· cyclohexyl group in position 3 is stable under these conditions, the monobromo-derivative must have the structure (XXVI).

Bromination experiments were also performed with aposafranone and some of its derivatives. Under the same conditions of bromination, aposafranone gave a monobrominated derivative which was converted by warm aniline into anilinoaposafranone (XXVIII). It seems probable, therefore, that structure (XXVII) represents the monobromo-compound. Anilinoaposafranone (XXVIII), however, gave a tetrabromo-derivative from which treatment with cyclohexylamine eliminated one bromine atom, yielding a tribromo-compound. For reasons already given we consider that this bromine atom has been removed from a bromoimino-grouping. The positions of two of the remaining bromine atoms have been fixed by brominating the 2,4-dibromoanilinoaposafranone (XXIX), which had been synthesised unambiguously by condensation of aposafranone with 2,4-dibromoaniline. Bromination of the dibromo-compound (XXIX) gave the same tetrabromo-derivative as was already obtained by direct bromination of anilinoaposafranone (XXVIII). The fourth bromine atom has probably substituted the 6-position of the anilino-group. It was not possible to confirm this as 2,4,6-tribromoaniline could not be condensed with aposafranone. The tri- and tetra-bromoanilinoaposafranone are formulated as (XXX) and (XXXI).

Experimental

Light petroleum had b. p. 40—60°; ligroin had b. p. 100—120°.

Bromination of Anilinoaposafranine.—A solution of bromine (2·5 c.c.) in chloroform (10 c.c.) was added dropwise with stirring to anilinoaposafranine (2·0 g.) in chloroform (200 c.c.). The solution, when kept for 3 hr., deposited dark green crystals which were suspended in ethanol and treated with dilute sodium hydroxide solution. The base was purified chromatographically on alumina. *3-Bromoimino-3,5-dihydro-5-phenyl-2-(N,2,4-tribromoanilino)phenazine* (1·0 g.) (III) was obtained as bronze glistening needles (from benzene), m. p. >310° (Found: C, 44·1; H, 2·1; N, 8·4; Br, 46·0. $C_{24}H_{14}N_4Br_4,\frac{1}{2}C_6H_6$ requires C, 44·3; H, 2·3; N, 8·0; Br, 45·5%). Its solution in concentrated sulphuric acid has a deep blue colour which changes to red on dilution.

Heating of Tetrabromoanilinoaposafranine.—(a) *With cyclohexylamine.* The hydrochloride of the bromo-compound (1·0 g.) was heated under reflux with cyclohexylamine (25·0 c.c.) for ½ hr. Excess of amine was steam-distilled and the residue purified on an alumina column. *3-Bromoimino-2-(2,4-dibromoanilino)-3,5-dihydro-5-phenylphenazine* (IV) was obtained as dark

red needles (from benzene–methanol), m. p. 210° (decomp.) (0·4 g.) (Found: C, 48·6; H, 2·7; N, 9·3; Br, 39·7. $C_{24}H_{15}N_4Br_3$ requires C, 48·1; H, 2·5; N, 9·3; Br, 40·1%). Its solution in concentrated sulphuric acid is petunia-purple.

(b) *With aniline.* The product which crystallised from the chloroform solution above was heated under reflux with aniline for 15 min. The solution was poured into ether, and the precipitated salts converted into the base which was purified on alumina. 2-Anilino-3,5-dihydro-5-phenyl-3-phenyliminophenazine (II) was obtained as dark red needles, m. p. and mixed m. p. 234—236°.

(c) *With ethanolic sulphuric acid.* Tetrabromoanilinoaposafranine (0·8 g.), ethanol (10·0 c.c.), and dilute sulphuric acid (5·0 c.c.) were heated in a sealed tube at 160—170° for 4 hr. The mixture was made alkaline with dilute sodium hydroxide solution. The precipitate was washed repeatedly with warm dilute alkali, and the residue was chromatographed in benzene on alumina. The eluate was evaporated to dryness and the residue recrystallised from ethanol, yielding 2,4-dibromoanilinoaposafranone (50 mg.) (XXIX), m. p. 257—258° not depressed on admixture with an authentic sample (see below).

The combined alkaline extracts were acidified with acetic acid, giving the orange-yellow flocculent precipitate of hydroxyaposafranone.[2]

3-*Bromoimino*-2-(N,2-*dibromo*-4-*chloroanilino*)-5-p-*chlorophenyl*-3,5-*dihydrophenazine* (VI).—2-*p*-Chloroanilino-5-*p*-chlorophenyl-3,5-dihydro-3-iminophenazine (V) (1·2 g.) was brominated, and the product purified, as described for anilinoaposafranine. The *tribromo-compound* was obtained as red-brown needles (0·3 g.) (from benzene), m. p. >320° (Found: C, 44·3; H, 1·9; N, 8·3; Cl, 10·4; Br, 35·4. $C_{24}H_{13}N_4Cl_2Br_3,\frac{1}{2}C_6H_6$ requires C, 44·5; H, 2·1; N, 8·1; Cl, 10·3; Br, 34·9%). This bromo-compound (0·3 g.) on refluxing with cyclohexylamine yielded 2-(2-*bromo*-4-*chloroanilino*)-3-*bromoimino*-5-p-*chlorophenyl*-3,5-*dihydrophenazine* (VII), an orange-brown powder (0·1 g.) (from benzene–methanol), m. p. 206° (decomp.) (Found: C, 49·8; H, 2·5; N, 9·3; Cl, 11·7; Br, 26·5. $C_{24}H_{14}N_4Cl_2Br_2$ requires C, 48·9; H, 2·4; N, 9·5; Cl, 12·1; Br, 27·2%).

3-*Cyclohexylimino*-3,5-*dihydro*-5-*phenyl*-2-(N,2,4-*tribromoanilino*)*phenazine* (IX; R = cyclohexyl).—2-Anilino-3-cyclohexylimino-3,5-dihydro-5-phenylphenazine (VIII; R = cyclohexyl) (1·3 g.) in chloroform (16 c.c.) was stirred during the dropwise addition of bromine (1 c.c.) in chloroform (8 c.c.). The solution was kept overnight, ligroin added, and the precipitate converted into the base with ethanolic ammonia. The *base* was purified on alumina and obtained as a black powder (0·3 g.), m. p. 200—205° (decomp.) (from chloroform–ligroin) (Found: C, 52·7; H, 4·0; N, 7·7; Br, 36·0. $C_{30}H_{25}N_4Br_3$ requires C, 52·9; H, 3·7; N, 8·2; Br, 35·2%).

3-*Cyclohexylimino*-2-(2,4-*dibromoanilino*)-3,5-*dihydro*-5-*phenylphenazine* (IXa).—The hydrochloride of the tribromo-base (0·6 g.) (IX; R = cyclohexyl) was heated under reflux for 90 min. with cyclohexylamine (20 c.c.). The precipitate obtained with methanol was chromatographed in benzene on alumina, and the single band collected in two fractions. The second fraction was rechromatographed, and the second half of the eluate yielded the *dibromo-compound* as brown needles (0·1 g.), m. p. 222—224° (Found: C, 60·3; H, 4·4; N, 9·2; Br, 25·9. $C_{30}H_{26}N_4Br_2$ requires C, 59·8; H, 4·3; N, 9·3; Br, 26·6%).

5-p-*Chlorophenyl*-2-(N,2-*dibromo*-4-*chloroanilino*)-3,5-*dihydro*-3-*isopropyliminophenazine* (XII).—2-*p*-Chloroanilino-5-*p*-chlorophenyl-3,5-dihydro-3-isopropyliminophenazine (X) (5·0 g.) in chloroform (300 c.c.) was treated dropwise with bromine (3 c.c.) in chloroform (20 c.c.). The *product* (5·2 g.), purified as above, was obtained as dark red needles, m. p. 193—195° (decomp.) (from benzene) (Found: C, 51·4; H, 3·2; N, 8·9; Cl, 11·2; Br, 25·4. $C_{27}H_{20}N_4Cl_2Br_2$ requires C, 51·3; H, 3·2; N, 8·9; Cl, 11·3; Br, 25·4%).

2-(2-*Bromo*-4-*chloroanilino*)-5-p-*chlorophenyl*-3,5-*dihydro*-3-*isopropyliminophenazine* (XIV).—The hydrochloride of the dibromo-base (XII) (2·0 g.) was heated under reflux with cyclohexylamine (25 c.c.) for 1 hr. The excess of cyclohexylamine was steam-distilled and the product (0·2 g.) purified chromatographically. The *monobromo-compound* was obtained as red-brown needles, m. p. 205—208° (from benzene–ligroin) (Found: C, 59·9; H, 4·2; N, 9·7; Cl, 12·6; Br, 14·1. $C_{27}H_{21}N_4Cl_2Br,\frac{1}{4}C_6H_6$ requires C, 60·2; H, 4·0; N, 9·7; Cl, 12·3; Br, 13·9%).

5-o-*Chlorophenyl*-2-(N,4-*dibromo*-2-*chloroanilino*)-3,5-*dihydro*-3-*isopropyliminophenazine* (XIII).—2-*o*-Chloroanilino-5-*o*-chlorophenyl-3,5-dihydro-3-isopropyliminophenazine (XI) (1·0 g.) gave with the usual treatment the *dibromo-base* (0·3 g.), m. p. 200° (decomp.) (from benzene–methanol) (Found: C, 51·5; H, 3·2; N, 9·1; Cl, 11·1; Br, 25·1. $C_{27}H_{20}N_4Cl_2Br_2$ requires C, 51·3; H, 3·2; N, 8·9; Cl, 11·3; Br, 25·4%).

XUM

2-(4-*Bromo*-2-*chloroanilino*)-5-o-*chlorophenyl*-3,5-*dihydro*-3-*isopropyliminophenazine* (XV).—The hydrochloride of the dibromo-base (XIII) (0·2 g.) with the usual cyclohexylamine treatment gave the *monobromo-compound* (50 mg.), m. p. 231—233° (from benzene–methanol) (Found: C, 60·1; H, 4·2; N, 9·5; Cl, 12·0; Br, 13·7. $C_{27}H_{21}N_4Cl_2Br$ requires C, 60·9; H, 4·1; N, 9·5; Cl, 12·0; Br, 13·5%).

3,5-*Dihydro*-3-*isopropylimino*-5-*phenyl*-2-(N,2,4-*tribromoanilino*)*phenazine* (IX; R = Pr^i) (0·3 g.) was obtained by the usual bromination method from 2-anilino-3,5-dihydro-3-isopropylimino-5-phenylphenazine (VIII; R = Pr^i) (1·1 g.). It was a black powder, m. p. 200—201° (decomp.) (from ethanol) (Found: C, 50·8; H, 3·4; N, 8·6; Br, 37·5. $C_{27}H_{21}N_4Br_3$ requires C, 50·5; H, 3·3; N, 8·7; Br, 37·4%).

3,5-*Dihydro*-5-*phenyl*-3-*t*-*butylimino*-2-(N,2,4-*tribromoanilino*)*phenazine* (IX; R = Bu^t) (0·1 g.) was obtained by the bromination of 2-anilino-3,5-dihydro-5-phenyl-3-t-butyliminophenazine (VIII; R = Bu^t) (0·35 g.). It formed dark green needles, m. p. 218—220° (from benzene–ethanol) (Found: C, 51·3; H, 3·8; N, 8·7; Br, 37·0. $C_{28}H_{23}N_4Br_3$ requires C, 51·3; H, 3·5; N, 8·5; Br, 36·6%).

4,5-*Di*-p-*bromoanilino*-o-*quinone*.—Catechol (2·2 g.) and *p*-bromoaniline (6·8 g.) were dissolved in ethanol (150 c.c.) and sodium iodate (4·4 g.) in water (150 c.c.) added. The mixture was stirred for 3 hr. and kept overnight. The bright red *quinone* (5·1 g.) which separated had m. p. 245—247° (from chloroform) (Found: C, 48·2; H, 2·6; N, 6·2; Br, 36·1. $C_{18}H_{12}O_2N_2Br_2$ requires C, 48·2; H, 2·7; N, 6·3; Br, 35·7%).

2-p-*Bromoanilino*-3-p-*bromophenylimino*-3,5-*dihydro*-5-*phenylphenazine* (XVI).—The above quinone (4·9 g.) and 2-aminodiphenylamine hydrochloride (2·5 g.) were heated under reflux with ethanol (200 c.c.) for 2 hr. The mixture on treatment with excess of dilute ammonia gave, after chromatographic purification, brown needles (2·0 g.) (from benzene), m. p. 235—236° (Found: C, 60·7; H, 3·4; N, 9·5; Br, 26·7. $C_{30}H_{20}N_4Br_2$ requires C, 60·4; H, 3·4; N, 9·4; Br, 26·8%). Bromination of the above compound, or of 2-anilino-3,5-dihydro-5-phenyl-3-phenyliminophenazine (II), gave 3-p-*bromophenylimino*-3,5-*dihydro*-5-*phenyl*-2-(N,2,4-*tribromoanilino*)*phenazine* (XVII). It formed almost black needles, m. p. >310° (from benzene) (Found: C, 47·5; H, 2·4; N, 7·1; Br, 42·6. $C_{30}H_{18}N_4Br_4$ requires C, 47·7; H, 2·4; N, 7·4; Br, 42·4%). The identity of the two products was established by examination in the infrared region, and by their blue colour in concentrated sulphuric acid. The tetrabromo-compound (0·4 g.) was heated for 1 hr. with cyclohexylamine (20 c.c.) and cyclohexylamine hydrochloride (0·4 g.). The solution was diluted with methanol and kept overnight. The precipitate was purified in benzene in an alumina column, yielding brown needles (0·1 g.), m. p. 265—267° (from benzene–methanol) (Found: C, 48·1; H, 2·3; N, 7·4; Br, 41·7. $C_{30}H_{18}N_4Br_4$ requires C, 47·7; H, 2·4; N, 7·4; Br, 42·4%). This compound is isomeric with the starting material and probably has the structure (XXIV). It has a violet colour in concentrated sulphuric acid. Repetition of this experiment has always given mixtures which we have failed to purify by chromatography. For example one product, m. p. 242—244° (from benzene–methanol), had C, 51·1; H, 2·8; N, 8·4; Br, 38·4 ($C_{30}H_{19}N_4Br_3$ requires C, 53·3; H, 2·8; N, 8·3; Br, 35·6%).

2-*Bromoamino*-3-p-*bromophenylimino*-3,5-*dihydro*-5-*phenylphenazine* (XXIII).—2-Amino-3,5-dihydro-5-phenyl-3-phenyliminophenazine (XVIII) (2·4 g.) by the usual bromination method gave the *dibromo-base* as dark red needles (1·6 g.), m. p. 242—244° (from benzene) (Found: C, 57·6; H, 3·2; N, 10·0; Br, 28·9. $C_{24}H_{16}N_4Br_2,\frac{1}{2}C_6H_6$ requires C, 57·9; H, 3·6; N, 10·0; Br, 28·6%). Boiling this compound with acetic anhydride gave unaltered material. When heated under reflux for 25 min. with aniline (25 c.c.) and aniline hydrobromide (0·6 g.), and purified as described earlier, 0·7 g. of the dibromo-base (XXIII) yielded the bromine-free compound (II).

2-*Bromoamino*-5-*cyclohexyl*-3-*cyclohexylimino*-3,5-*dihydrophenazine* (XXII) (0·3 g.), m. p. 225—227° (from ethanol) (Found: C, 63·7; H, 6·4; N, 12·4; Br, 17·6. $C_{24}H_{29}N_4Br$ requires C, 63·6; H, 6·4; N, 12·4; Br, 17·7%), was obtained by bromination of the amino-compound (XX) (0·4 g.). Similarly the *p*-chlorophenyl analogue (XIX) gave, on bromination, 2-*bromoamino*-5-p-*chlorophenyl*-3-p-*chlorophenylimino*-3,5-*dihydrophenazine* (XXI) in 50% yield. It formed red needles, m. p. 278—280° (from benzene-methanol) (Found: C, 56·5; H, 3·0; N, 11·1; Cl, 14·1; Br, 15·8. $C_{24}H_{15}N_4Cl_2Br$ requires C, 56·5; H, 2·9; N, 11·0; Cl, 13·9; Br, 15·7%).

2-*Bromoamino*-3-*cyclohexylimino*-3,5-*dihydro*-5-*phenylphenazine* (XXVI) (0·15 g.) was obtained by bromination of 2-cyclohexylamino-3-cyclohexylimino-3,5-dihydro-5-phenylphenazine

(XXV) (0·4 g.). It formed orange-yellow needles, m. p. 235—237° (from ethanol–benzene) (Found: C, 64·2; H, 4·9; N, 12·2; Br, 17·8. $C_{24}H_{23}N_4Br$ requires C, 64·4; H, 5·1; N, 12·5; Br, 17·9%). This decomposes on the alumina column.

2-Bromo-3,5-dihydro-3-oxo-5-phenylphenazine (XXVII) was got in 60% yield by bromination of aposafranone. It was a dark brown powder, m. p. 228—230° (from ethanol) (Found: C, 61·1; H, 3·1; N, 8·3; Br, 22·0. $C_{18}H_{11}ON_2Br$ requires C, 61·5; H, 3·1; N, 8·0; Br, 22·8%). Its solution in concentrated sulphuric acid is vivid green, becoming amber-coloured on dilution. The hydrobromide of this compound when heated with aniline for 4 hr. on the water-bath yielded anilinoaposafranone (XXVIII).

2,4-Dibromoanilinoaposafranone (XXIX).—Aposafranone (0·7 g.), 2,4-dibromoaniline hydrochloride (1·0 g.), and 2,4-dibromoaniline (1·8 g.) were heated together on the water-bath for 3 hr. The product was recrystallised from benzene–ligroin, to give *2-(2,4-dibromoanilino)-3,5-dihydro-3-oxo-5-phenylphenazine* (XXIX) as a red-brown powder (0·4 g.), m. p. 257—259° (Found: C, 57·0; H, 2·8; N, 8·0; Br, 29·6. $C_{24}H_{15}ON_3Br_2,\frac{1}{2}C_6H_6$ requires C, 57·0; H, 3·1; N, 7·7; Br, 29·3%). On bromination this compound gave the tetrabromo-derivative (XXXI), *3,5-dihydro-3-oxo-5-phenyl-2-(N,2,4,6-tetrabromoanilino)phenazine*, as a red powder, m. p. 205—206° (from ligroin–benzene) (Found: C, 44·6; H, 2·2; N, 6·0; Br, 45·5. $C_{24}H_{13}ON_3Br_4,\frac{1}{2}C_6H_6$ requires C, 44·3; H, 2·1; N, 6·0; Br, 45·4%). This tetrabromo-derivative (XXXI) was also got by direct bromination of anilinoaposafranone.

Treatment of Tetrabromoanilinoaposafranone (XXXI) *with Cyclohexylamine.*—The base (0·1 g.) was heated under reflux for 90 min. with cyclohexylamine (12 c.). The product obtained from the cooled solution on addition of methanol was obtained as red-brown crystals (80 mg.) (from benzene–methanol), m. p. 236—237° (Found: C, 48·7; H, 2·3; N, 6·8; Br, 39·8. $C_{24}H_{14}ON_3Br_3$ requires C, 48·0; H, 2·3; N, 7·0; Br, 40·0%). *3,5-Dihydro-3-oxo-5-phenyl-2-(2,4,6-tribromoanilino)phenazine* (XXX) is purple-red in concentrated sulphuric acid, becoming grey-green on dilution.

Grateful acknowledgment is made to J. R. Geigy, S.A., Basle, Switzerland, for financial aid, to Dr. H. Wagner of this firm for carrying out the analyses, and to Mr. E. R. Stuart, University Chemical Laboratory, for the infrared spectrophotometric examination.

Laboratories of the Medical Research Council of Ireland,
Trinity College, Dublin. [*Received, April 16th,* 1959.]

---

653. *The Structure of Floridean Starch. Part I. Linkage Analysis by Partial Acid Hydrolysis.*

By Stanley Peat, J. R. Turvey, and J. M. Evans.

We have isolated the Floridean starch of *Dilsea edulis* completely free from the accompanying galactan sulphate. The starch has been submitted to partial acid hydrolysis; isolation from the hydrolysate of isomaltose and trisaccharides containing the α-1 : 6-glucosidic link demonstrates that the main branch linkage in this polysaccharide is the same as it is in amylopectin and glycogen.

Conclusive evidence is afforded of the presence in the hydrolysate, in small quantity, of nigerose. Furthermore, nigerose was detected in the partial acid hydrolysate of the trisaccharide fragments. This is strong indication that the α-1 : 3-glucosidic link is an integral part of the structure of this starch, since the nigerose is produced in greater amounts than would be expected by reversion synthesis.

The constitution of Floridean starch, the iodophilic polysaccharide present in red algæ (*Rhodophyceae*), has been much investigated. Early workers [1,2] showed that this glucan was present in granular form in the algæ, that it was stained by iodine (red to violet), and

[1] Kylin, *Z. physiol Chem.*, 1913, **83**, 171; 1915, **94**, 337.
[2] Colin and Augier, *Compt. rend.*, 1933, **197**, 423.

XUM

was hydrolysed by malt diastase to maltose. Although some evidence suggested that the starch might contain 1 : 3- in addition to 1 : 4-linkages,[3] it was later shown that few, if any, 1 : 3-linkages were present.[4,5] That the starch did not consist entirely of α-1 : 4-linkages was indicated by the incomplete (*ca.* 50%) conversion into maltose by β-amylase.[4,6] More recently, periodate oxidation of Floridean starch has suggested that the repeating chain unit consists of 9 glucose members joined by 1 : 4-linkages and that the interchain, *i.e.*, branch, linkages are α-1 : 6-glucosidic, since isoamylase (an α-1 : 6-glucosidase from yeast) increased the β-amylolysis limit.[7]

This communication describes a structural analysis of Floridean starch by partial acid hydrolysis and identification of the oligosaccharide fragments. A preliminary account has already been published.[8]

Properties of the products of partial hydrolysis of Floridean starch.

Sugar	Yield [a] (g.)	$[\alpha]_D$ [b]	Acetyl derivative [b] $[\alpha]_D$	Acetyl derivative [b] m. p.
Glucose	4·97	+52·4° (52·6°)	+101·7° (101·6°)	112—113° (114°)
Maltose	1·69	+134·5 (136)	+63·1 (62·7)	158—159 (159—160)
Isomaltose	0·289	+123·8 (120—122)	+96·9 (97·8)	142—143 (143) [c]
Nigerose	0·035	+136 (136—139)	+86·6 (80—85)	147—148 (149—153) [c]
Panose	0·087	+152·5 (154)	+118·5 (120) [d]	147—148 (148—150) [c,d]
6-*O*-α-Maltosylglucose	0·079	+148·4		

[a] From 12·5 g. of Floridean starch. [b] Other reported values are given in parentheses. [c] Undepressed on admixture with an authentic specimen. [d] Panitol dodeca-acetate.

The Floridean starch, which was isolated by Lawley [6] from *Dilsea edulis*, contained a galactan sulphate. Selective precipitation [9] of the starch with iodine gave a galactan-free product but there was some loss of starch, more of which was isolated by selective precipitation of the galactan sulphate with cetyltrimethylammonium bromide. This reagent forms insoluble complexes with many acidic polysaccharides but does not precipitate neutral polysaccharides such as starch from aqueous solutions.[10] This procedure also gave a galactan-free product and the two samples were combined for subsequent examination. The product contained 92·6% of polyglucose as determined by acid hydrolysis, and paper chromatography of the hydrolysate indicated the presence of glucose only. An aqueous solution had $[\alpha]_D$ +173° (as $C_6H_{10}O_5$, +187°), a value similar to that found by Lawley [6] but higher than other reported values (+105° to +163°),[2,3,7] and akin to that of the glycogens (184—201°).[11]

The starch was hydrolysed in 0·33N-sulphuric acid at 100° to an apparent conversion (into glucose) of 53% (130 min.), and the products were fractionated by chromatography on charcoal–Celite. The only monosaccharide eluted was glucose. The disaccharides were eluted in two major fractions, the first consisting mainly of isomaltose, which was separated from minor contaminants and characterised (see Table). The second disaccharide fraction contained much maltose but a small amount of another disaccharide was also detected. The latter was separated from maltose by use of its higher electrophoretic mobility than that of maltose in borate buffer. Glucose oligosaccharides having the reducing-end glucose unit linked at $C_{(3)}$ or $C_{(6)}$ will have [12] a higher electrophoretic mobility (M_G value) in borate buffer than have those with the end unit linked at

[3] Barry, Halsall, Hirst, and Jones, *J.*, 1949, 1468.
[4] O'Colla, *Proc. Roy. Irish Acad.*, 1953, **55**, *B*, 321.
[5] Barry, McCormick, and Mitchell, *J.*, 1954, 3692.
[6] Lawley, Ph.D. Thesis, Wales, 1955.
[7] Fleming, Hirst, and Manners, *J.*, 1956, 2831.
[8] Peat, Turvey, and Evans, *Nature*, 1957, **179**, 261.
[9] Steiner and Guthrie, *Ind. Eng. Chem. Anal. Edn.*, 1944, **16**, 736.
[10] Scott, *Chem. and Ind.*, 1955, 168.
[11] Manners and Ryley, *Biochem. J.*, 1955, **59**, 369.
[12] Foster, *Adv. Carbohydrate Chem.*, 1957, **12**, 81.

$C_{(2)}$ or $C_{(4)}$. The minor disaccharide component with high M_G value would thus appear to be either a 1 : 3- or a 1 : 6-linked diglucose. Comparison with the R_F values of isomaltose, gentiobiose, and laminaribiose made it unlikely that the diglucose was any of these. This strong indication that the minor disaccharide is nigerose was confirmed by a comparison of the properties of the sugar and its acetyl derivative with those of authentic nigerose. The yields of nigerose (34·6 mg.) and isomaltose (289 mg.) from Floridean starch (12·5 g.) are many times larger than would be expected by acid reversion from an equivalent weight of glucose (2 mg. and 7 mg., respectively).[13] However, as pointed out previously,[13] the amounts of acid reversion products arising from glucose may not be the same as those arising from a similar weight of an oligosaccharide treated under the same conditions (see later).

The trisaccharide components of the partial hydrolysate were eluted from the column in two main portions, each of which was a mixture. The first mixture migrated as a single substance with the R_F value of 4-*O*-α-isomaltosylglucose (panose) on a paper chromatogram, but was resolved into two trisaccharides by preparative paper electrophoresis in borate buffer. The component with lower M_G value was identified as panose and that with higher M_G value as 6-*O*-α-maltosylglucose (Table), both of which have been obtained by partial acid hydrolysis of potato starch and of yeast glycogen.[14,15] Confirmation of these structures was furnished by reduction with sodium borohydride, partial acid hydrolysis of the trisaccharide alcohols so produced, and chromatographic identification of the derived disaccharides and alcohols. Thus panose gave a mixture of isomaltose and maltitol as the only " disaccharides " and 6-*O*-α-maltosylglucose gave maltose and isomaltitol. The second portion of the original eluate was collected in two parts, *A* and *B*, each of which contained maltotriose, but differed in their content of other trisaccharides. Mixture *A* was separated by paper electrophoresis into two fractions having high and low M_G values (A_H and A_L respectively). Fraction A_L (150 mg.) was shown by paper chromatography to consist of sugars with the R_F value of the main constituent, maltotriose, and it was slowly hydrolysed to a mixture of maltose and glucose by β-amylase, a characteristic of maltotriose. Partial acid hydrolysis of A_L showed however that the maltotriose was not pure, since isomaltose and nigerose, in addition to maltose, were detected in the hydrolysate. The presence of isomaltose in the hydrolysate of A_L, coupled with the low M_G value of this fraction, indicated that a trisaccharide containing an α-1 : 6-linkage with an α-1 : 4-linkage at the reducing end was present in the mixture. Two trisaccharides fulfil this requirement, namely 4-*O*-α-isomaltosylglucose and 4 : 6-di-*O*-glucosylglucose. The former, panose, can be eliminated as a possibility on the grounds that this sugar has a different R_F value from that of maltotriose and would therefore not be found in the mixture A_L. Consequently it is inferred that the " branched " trisaccharide 4 : 6-di-*O*-α-glucosylglucose is a constituent of mixture A_L. Similar evidence for the presence of this trisaccharide in acid hydrolysates of potato starch has previously been recorded.[14] Mixture *B* was also resolved by paper electrophoresis into two fractions with high and low M_G values (B_H and B_L respectively). Fraction B_L (254 mg.) was examined by the method outlined for fraction A_L, and gave similar results except that more nigerose and less isomaltose were detected in a partial acid hydrolysate of the fraction. The derivation of significant amounts of nigerose from A_L and B_L is an indication of the presence of the trisaccharide, 4-*O*-α-nigerosylglucose, in these fractions. It is improbable that nigerose was produced by reversion synthesis from the trisaccharides during acid hydrolysis, since it has been found that the partial hydrolysis of such trisaccharides as panose and 6-*O*-α-maltosylglucose does not give rise to nigerose.

Fractions A_H and B_H were combined and examined by the same procedure. The combined fraction had an R_F value similar to that of maltotriose but had a high M_G value

[13] Peat, Whelan, Edwards, and Owen, *J.*, 1958, 586.
[14] Edwards, Ph.D. Thesis, Wales, 1955.
[15] Peat, Whelan, and Edwards, *J.*, 1955, 355.

XUM

indicating the presence of 3- or 6-linked reducing end units. The disaccharide components of the partial acid hydrolysate were maltose, isomaltose, and nigerose, the last two being present in greater amounts than was the maltose, as judged by visual examination of paper chromatograms.

The conclusion is reached that Floridean starch is structurally related to glycogen or amylopectin inasmuch as the main polymeric linkage is α-1 : 4-glucosidic and that a small proportion of α-1 : 6-linkages also occurs. The isolation of panose and 6-*O*-α-maltosylglucose, and the inferred presence of 4 : 6-di-*O*-α-glucosylglucose in the hydrolysate, support the view that the 1 : 6-linkages constitute points of branching. Furthermore, the isolation of nigerose and of trisaccharides containing α-1 : 3-linkages indicates the presence of a small, but significant, proportion of these linkages in the structure. It is to be noted that small proportions of α-1 : 3-linkages have been reported in waxy-maize starch and calf-liver glycogen.[16] It is not yet known whether the nigerose and related trisaccharides isolated could be entirely the products of acid reversion but the balance of evidence is against this view. First, no trisaccharides have been detected as reversion products when glucose is treated with acid under similar conditions, and the disaccharides produced from glucose by reversion are mixtures of α- and β-isomers whereas no saccharides containing β-linkages have been detected in this study. Secondly, as reported in the following communication, nigerose has been found also in enzymic hydrolysates of Floridean starch.

Experimental

General Methods.—Paper chromatography was conducted in the solvent systems (*a*) butan-1-ol–acetic acid–water (4 : 1 : 5; by vol.) and (*b*) butan-1-ol–pyridine–water (6 : 4 : 3; by vol.) as described by Peat *et al.*[17] With solvent (*a*) nigerose can be detected in presence of maltose and isomaltose; with (*b*) isomaltose in the presence of maltose and nigerose, and panose in the presence of maltotriose. Paper electrophoresis, determination of specific optical rotations, and partial acid hydrolysis of oligosaccharides were carried out as described by Peat *et al.*[17] The determination of the polyglucose content of the starch was as described by Pirt and Whelan.[18] Acetyl derivatives were prepared by the sodium acetate–acetic anhydride method unless otherwise stated.

Purification of Floridean Starch.—The sample (79 g.) was isolated by Lawley [6] from *Dilsea edulis* using the method of Barry *et al.*[3] As it was contaminated with a galactan, it was treated in 1 g. portions by the iodine-precipitation method.[9] Complete acid hydrolysis of the product (22 g.) gave glucose alone. The polysaccharide not precipitated by iodine was recovered by addition of N-sodium thiosulphate to remove excess of iodine and precipitation in ethanol (3 vol.); it still contained some starch as indicated by the iodine stain. This starch was isolated by adding to an aqueous solution (2% w/v), a solution of cetyltrimethylammonium bromide (4% w/v) until the point of flocculation of the complex [10] was reached. The precipitate was removed by centrifugation and the supernatant solution was freed from excess of reagent by repeated extraction with chloroform. The aqueous layer was poured into ethanol (3 vol.), and the precipitated starch washed with ethanol and ether and dried over phosphoric oxide. Complete acid hydrolysis of a small portion confirmed that the product (5 g.) contained no galactan. The combined starch fractions contained 15% of ash. Accordingly, the starch (27 g.) was dissolved in hot water (1 l.), dialysed against running water for 72 hr., recovered by pouring into ethanol (3 vol.), and dried as before. The Floridean starch (20 g.) contained 0·25% of ash, 0·24% of nitrogen, and 92·6% of polyglucose, and had $[\alpha]_D^{18}$ +173° (*c* 0·1 in water).

Partial Hydrolysis of Floridean Starch and Fractionation of the Products.—A solution of the starch (12·5 g.) in 0·33N-sulphuric acid (1·25 l.) was heated on a boiling-water bath. After 130 min., the apparent conversion into glucose was 53%, as measured by the copper-reducing power of a sample. After neutralisation (sodium hydroxide) and concentration to 800 ml., the hydrolysate was adsorbed on charcoal–Celite (112 × 5 cm.), which was eluted with water (4·4 l.), 7·5% aqueous ethanol (8·2 l.), and 15% aqueous ethanol (8 l.), in that order. The

[16] Wolfrom and Thompson, *J. Amer. Chem. Soc.*, 1956, **78**, 4116; 1957, **79**, 4214.
[17] Peat, Whelan, and Roberts, *J.*, 1957, 3916.
[18] Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224.

course of the elution was followed by collecting fractions (*ca.* 200 ml. each) and measuring their optical rotations (4 dm. tube). Fractions were combined as experience suggested and evaporated to dryness at pH 6—6·5, and the residue dissolved in hot 80% methanol, and the solution filtered and re-evaporated to dryness.

Examination of Hydrolysis Products.—(a) *Monosaccharides.* The only sugar eluted by water (fractions 10—24) was glucose (4·97 g.), identified by R_F value and by preparation of the α-acetyl derivative (acetic anhydride–perchloric acid method).

(b) *Disaccharides.* Two main products were eluted by 7·5% ethanol. The first (fractions 40—48) consisted of isomaltose with traces of glucose and maltose. Fractionation by preparative paper electrophoresis furnished pure isomaltose, a portion of which was acetylated (see Table). The second (fractions 49—64) when fractionated by preparative paper chromatography and electrophoresis furnished two sugars with the R_F and M_G values of maltose and nigerose, the latter being present mainly in the later fractions (52—64) of this batch. Each sugar was acetylated and the properties are reported in the Table.

(c) *Trisaccharides.* Two products were eluted by 15% ethanol. The first consisted mainly of a sugar with the R_F value of panose. After removal of traces of maltotriose by paper chromatography, the panose zone was resolved by preparative paper electrophoresis into zones of high and low M_G values. Partial acid hydrolysis of a small portion of each indicated that each yielded maltose and isomaltose. Reduction of small portions (7—8 mg.) with sodium borohydride,[15] followed by partial acid hydrolysis and paper-chromatographic identification of the disaccharides liberated indicated that the trisaccharide with the low M_G value gave isomaltose and maltitol, while that with the high M_G value gave maltose and isomaltitol. These are the products expected from panose and 6-*O*-α-maltosylglucose, respectively. The panose was further characterised by reduction to panitol and preparation of the acetyl derivative [15] (Table).

The second trisaccharide band was further separated into *A* (fractions 87—91) and *B* (fractions 92—99), each of which contained sugars with the R_F value of maltotriose but which were separated by paper electrophoresis into minor components, A_H and B_H, with high M_G value, and major components A_L (520 mg.) and B_L (284 mg.) of low M_G value. Portions of A_L and B_L (5 mg. each) were incubated separately with purified soya bean β-amylase [19] (4000 units) in 0·02M-acetate buffer (pH 4·8; 5 ml.) for 3 days at 35° under toluene. Paper chromatography of the hydrolysates indicated glucose and maltose in both, in addition to unchanged trisaccharide. Examination of the partial acid hydrolysate of each by paper chromatography and electrophoresis showed that the disaccharides consisted of isomaltose and nigerose in addition to the main component, maltose, and that fraction A_L gave more isomaltose than nigerose, while the reverse was true for fraction B_L. Fractions A_H and B_H were combined (37 mg.) and examined by partial acid hydrolysis. The disaccharides produced by hydrolysis again consisted of a mixture of maltose, isomaltose, and nigerose, but visual examination of the paper chromatograms indicated that isomaltose and nigerose were present in greater amounts than was the maltose.

We thank the Department of Scientific and Industrial Research for a grant to one of us (J. M. E.) and Dr. W. J. Whelan for helpful discussion.

UNIVERSITY COLLEGE OF NORTH WALES, BANGOR. [*Received, May 4th,* 1959.]

[19] Peat, Pirt, and Whelan, *J.*, 1952, 714.

654. *Kinetics of the Bromination of Acetone in Concentrated Aqueous Hydrochloric Acid.*

By G. Archer and R. P. Bell.

The rate of bromination (and hence of enolization) of acetone has been measured in 1—8M-aqueous hydrochloric acid. After correction for the proportion of acetone present in the protonated form the reaction velocity is found to depend much more closely on the acidity function than on the acid concentration, in contrast to expectations for this type of reaction. This result casts some doubt on the use of acidity-dependence as a criterion of mechanism.

The rate of bromination or iodination of ketones in dilute solutions of strong acids is independent of the concentration of halogen and directly proportional to that of hydrogen ions. The usually accepted mechanism is

$$>CH\cdot\dot{C}{:}O + H_3O^+ \rightleftharpoons >CH\cdot\dot{C}{:}\overset{+}{O}H + H_2O \quad \text{(fast)}$$

$$>CH\cdot\dot{C}{:}\overset{+}{O}H + H_2O \longrightarrow >C{:}\dot{C}\cdot OH + H_3O^+ \quad \text{(slow)}$$

followed by rapid halogenation of the enol. This mechanism is highly probable, since proton transfers to and from oxygen atoms are known to take place rapidly, and it is supported by the fact that the substitution of deuterium oxide for water increases the reaction velocity,[1] an effect which would be difficult to explain in any other way. Attempts have also been made to obtain evidence as to mechanism from measurements of reaction velocity at high concentrations of acid. According to a hypothesis first put forward by Zucker and Hammett,[2] if the transition state is formed simply by the addition of a proton to the substrate, then the reaction velocity will be closely proportional to the acidity function h_0, but if (as in the above mechanism) the transition state also contains a water molecule, then the reaction velocity will increase less rapidly than h_0 and may be approximately proportional to the hydrogen-ion concentration. The experimental evidence for the general validity of this distinction has been recently reviewed by Long and Paul.[3] The evidence relating to the enolization of ketones is rather meagre. Zucker and Hammett[4] studied the iodination of acetophenone in aqueous perchloric acid up to 3·6M, but found that at higher acidities the rate was no longer independent of iodine concentration. More recently, Satchell[5] has measured the rate of iodination of acetone in aqueous hydrochloric acid up to 2·7M. Both papers report that the reaction velocity is more closely proportional to $[H_3O^+]$ than to h_0, but the measurements do not extend to very high concentrations, and, as will be seen later, there are some problems about their interpretation. The present paper describes measurements of the rate of bromination of acetone in 1—8M-aqueous hydrochloric acid.

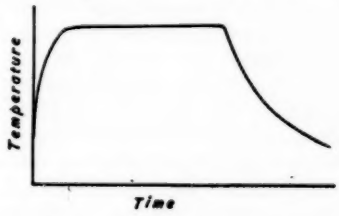
Experimental

All materials were of " AnalaR " grade, and hydrochloric acid solutions were standardized against borax. The course of the reaction was followed by observing the temperature change in the apparatus previously described for the thermal maximum method.[6,7] The reaction was started by breaking a small bulb of bromine solution in 50 c.c. of acetone solution, the concentration of hydrochloric acid being the same in both solutions. The concentration of acetone

[1] Reitz, *Z. Elektrochem.*, 1937, **43**, 659; *Z. phys. Chem.*, 1937, **179**, A, 119.
[2] Zucker and Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2785.
[3] Long and Paul, *Chem. Rev.*, 1957, **57**, 935.
[4] Zucker and Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2791.
[5] Satchell, *J.*, 1957, 2878.
[6] Bell and Clunie, *Proc. Roy. Soc.*, 1952, *A*, **212**, 16.
[7] Bell, Gold, Hilton, and Rand, *Discuss. Faraday Soc.*, 1954, **17**, 151.

was at least 50 times that of bromine, so that the reaction followed a zero-order course. The plots of galvanometer reading against time resembled the Figure, where the almost horizontal portion represents a steady state in which the rate of heat production by the reaction is equal to the rate of heat loss to the thermostat. The break in the curve corresponds to the point at which all the bromine is used up and the temperature begins to fall: in our experiments the first-order cooling constant was about 0·08 sec.$^{-1}$. Galvanometer readings were taken every 2 sec. and recorded by means of a dictaphone. The velocity constants were calculated from the time at which the break in the curve occurs: this varied between 30 and 100 sec., and could be located with an accuracy of 1—2 sec. Variations in bromine concentration by a factor of two produced no significant change in the velocity constants, thus confirming the zero-order character of the reaction.

Some of the earlier experiments showed poor reproducibility and gave curves differing in form from the Figure. This was traced to the formation in acid solutions of acetone of appreciable amounts of mesityl oxide, which reacts with bromine much more rapidly than does acetone. Mesityl oxide absorbs strongly at 243 mμ in aqueous solution ($\varepsilon = 8600$; in approximate agreement with earlier workers [8]), and this could be used to determine its concentration.



Its formation could be minimized by keeping the acetone concentration fairly low, and by adding the acetone to the acid solution only just before the addition of bromine. An interval of about 2 min. was necessary to attain thermal equilibrium, and tests showed that after this time the amount of mesityl oxide formed never exceeded 5% of the amount of bromine used in the reaction.

The experimental results are given in the first three columns of the Table. Each velocity

Rate of enolization (bromination) of acetone in aqueous hydrochloric acid at 25°.
k = first-order velocity constant in sec.$^{-1}$. c = concentration in moles/l.

c (acetone)	c (HCl)	10^5k	c (HCl) (corr.)	$-H_0$	$-\log\{k(K_{BH^+} + h_0)/h_0K_{BH^+}\}$
0·430	1·00	3·68	0·98	0·19	4·90
0·430	2·00	8·38	1·95	0·67	5·00
0·218	3·00	15·2	2·95	1·03	5·04
0·218	4·00	23·8	3·92	1·37	5·08
0·218	5·00	34·0	4·87	1·71	5·11
0·218	6·00	53·2	5·84	2·06	5·03
0·132	7·00	72·6	6·88	2·51	4·97
0·132	8·00	112	7·87	2·96	4·82

constant is the mean of three separate determinations, which had an average deviation of ±1%. The first-order constant for enolization is calculated on the assumption (justifiable under our conditions) that each molecule of acetone reacts with one molecule of bromine.

Discussion

The velocity constants in the Table are about 10% greater than those obtained by Dawson and Powis [9] in 1M-hydrochloric acid and by Satchell [5] in the range 1—3M. This discrepancy is somewhat greater than the estimated experimental uncertainties, and is probably due to formation of mesityl oxide. However, the uncertainty is not great enough to affect the general nature of the relation between rate and acid concentration.

[8] Nagakura, Minegishi, and Stanfield, *J. Amer. Chem. Soc.*, 1957, **79**, 1033.
[9] Dawson and Powis, *J.*, 1913, 2135.

XUM

If log k is plotted against H_0 or $-\log c$ neither plot is a straight line of unit slope, but the discrepancy is smaller for $-\log c$ than for H_0, in agreement with the findings of Zucker and Hammett [4] and of Satchell [5] at lower concentrations. However, this type of plot is appropriate only when the extent of protonation of the substrate is small, and this is certainly not the case at the acidities used in our experiments. Recent spectrophotometric measurements [8] give $pK_{SH^+} = -1{\cdot}58$ for the ion $Me_2C{:}OH^+$, and this value corresponds to a 5—95% protonation of acetone in 1—8M-hydrochloric acid. Under these conditions the observed velocity constants must be multiplied by $([S] + [SH^+])/[S]$ before comparison with the acidity function or the acid concentration, and if we make the assumptions about activity coefficients which are implicit in the acidity function concept this correction factor becomes $(K_{SH^+} + h_0)/K_{SH^+}$. A further small correction is necessary because the acid concentration is decreased by the formation of SH^+: the corrected acid concentrations are given in the fourth column of the Table, and the values of H_0 in the fifth column correspond to these corrected concentrations, the data collected by Paul and Long [11] being used.

If the corrected velocity constant is proportional to the acidity function h_0, then the quantity in the last column should be independent of concentration. It does in fact vary slightly, but shows no consistent trend with concentration. On the other hand, proportionality between the corrected velocity and the acid concentration should give a constant value to $-\log \{k(K_{SH^+} + h_0)/cK_{SH^+}\}$, and this quantity increases steadily by two logarithmic units as the concentration increases. Our results thus indicate that the reaction rate is related to the acidity function rather than to the acid concentration, in contrast to the accepted view for this type of reaction. If Satchell's results [5] are corrected in the same way for the protonation of the acetone they fall just half way between linear dependence on h_0 and on c, but the acid concentrations are not high enough for the deviations to be great.

Since the mechanism of acid-catalyzed enolization is well established [12] the above results throw considerable doubt upon the validity of Zucker and Hammett's hypothesis for reactions in which the transition state contains a water molecule. Similar conclusions have been reached on the basis of the effect of pressure on some acid-catalyzed reactions,[13] where the observed volume of activation suggests the mechanism A-2, while the parallelism with h_0 indicates A-1. This hypothesis admittedly has little theoretical basis, and has been put forward on the basis of experimental evidence. Our own results show that when there is a considerable degree of protonation the observed velocity constant may be approximately proportional to the acid concentration although the corrected velocity follows the acidity function closely, and it would be desirable to obtain direct evidence of the degree of protonation in other reactions which appear to follow the acid concentration. However, as pointed out by Long and Paul,[3] the effect of acid concentration on the reaction velocity may depend upon the part played by the water molecule in the transition state. In acid-catalyzed enolization it is acting as a base in removing a proton from the ≡CH group, while in other reactions (*e.g.*, the acid hydrolysis of esters) it becomes attached to carbon by a nucleophilic displacement. It may well be that these different modes of attack correspond to different behaviour in the activity coefficients of the transition state, but further experimental evidence is needed.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, May 12th*, 1959.]

[10] Long and Paul, reference 3; Schubert and Latourette, *J. Amer. Chem. Soc.*, 1952, **74**, 1829.
[11] Paul and Long, *Chem. Rev.*, 1957, **57**, 1.
[12] For recent confirmation by a study of deuterated ketones, see Swain, Di Milo, and Cordner, *J. Amer. Chem. Soc.*, 1958, **80**, 5983.
[13] Koskikallio and Whalley, *Trans. Faraday Soc.*, 1959, **55**, 815.

655. *The Decomposition of Nitramide in* m-*Cresol catalysed by Aniline Derivatives.*

By W. W. Carnie, P. M. Duncan, J. A. Kerr, Kathleen Shannon, A. F. Trotman-Dickenson, and J. A. White.

Decomposition of nitramide catalysed by primary, secondary, and tertiary aniline derivatives in *m*-cresol has been investigated between 9° and 55°. Activation energies for the catalytic coefficients have been determined. The catalytic coefficients at 25° are related to the activation energies by the expression E (kcal. mole^{-1}) = 15·0 − 0·135 $\log_{10} k_c$ (25°) (mole^{-1} kg. min.$^{-1}$). The significance of the findings is discussed.

Reactions that are catalysed by acids and bases are among the simplest of all chemical processes, at least in so far as their formal representation is concerned. The rate-determining steps of many of them consist solely of the transfer of a proton from one compound to another. In view of their simplicity, it is not surprising that they were the subject of one of the first generalisations of chemical kinetics, the Brönsted relation, which relates the catalytic coefficients of acids or bases to their dissociation constants.[1] The attempts that have been made to understand this free-energy relation have usually depended upon the assumption that the differences in the catalytic coefficients of different members of a class of compound are determined by the different heats of activation. The variations in the heats of activation were then explained in terms of potential-energy curves. Few attempts have been made to confirm this plausible interpretation by measurements of activation energies. Most activation energies have been measured in aqueous solution. It is not surprising that no simple relation has been found between the activation energies and catalytic coefficients in water. Ionic processes in water frequently fail to conform to the simplest types of energy relation.

This work was undertaken to extend that previously carried out on the decomposition of nitramide by aniline derivatives in anisole solution.[2] Anisole was chosen because it is a convenient solvent with which a considerable amount of work had been done. *m*-Cresol was chosen for the same reason, and had the further advantage that the value of the Brönsted coefficient, α, 0·84 for amines in *m*-cresol is considerably different from the corresponding value 0·64 for anisole. A marked difference in behaviour might therefore be expected. Caldin and Peacock [3] have, moreover, argued that there is some difference between hydroxylic and other solvents.

Experimental

Materials.—Some batches of the *m*-cresol (B.D.H.) were dried (P_2O_5–KOH) and fractionated on an 18" column packed with glass helices; some were simply fractionated, and other used as they were supplied. No difference in kinetic behaviour was detected. Aniline derivatives were usually distilled over potassium hydroxide under reduced pressure and stored in sealed containers. 3,4-Dichloroaniline was recrystallised from methanol. Nitramide was prepared by the method of Marlies, LaMer, and Greenspan.[4] As recommended by Ray and Ogg [5] the ethyl carbamate was, in the last two preparations, recrystallised from benzene, and the ammonium nitrourethane from methanol. The nitramide was dissolved in ether and precipitated with isopentane four times. If these precautions were not followed trouble was caused by an unknown catalytic impurity.

Apparatus and Procedure.—The runs were carried out in reaction vessels similar to Bell and Caldin's,[6] fitted with taps. Reaction mixtures were made up by weight. First, a convenient

[1] Bell, "Acid-Base Catalysis," Oxford, 1941.
[2] Fettis, Kerr, McClure, Slater, Steel, and Trotman-Dickenson, *J.*, 1957, 2811.
[3] Caldin and Peacock, *Trans. Faraday Soc.*, 1955, **51**, 1217.
[4] Marlies, LaMer, and Greenspan, *Inorg. Synth.*, 1939, **1**, 68.
[5] Ray and Ogg, *J. Phys. Chem.*, 1956, **60**, 1460.
[6] Bell and Caldin, *Trans. Faraday Soc.*, 1951, **47**, 50; Bell and Trotman-Dickenson, *J.*, 1949, 1288.

quantity of catalyst or catalyst solution was weighed in a weighing bottle. Sufficient hydrochloric acid was added to convert 5—10% of the base into its hydrochloride, to form a buffer solution. *m*-Cresol, to make approximately 2 g. of mixture, was then added. Finally, 2 c.c. of nitramide solution were added immediately before the mixture was introduced into the reaction vessel.

The increase in pressure of the evolved gas was observed. First-order plots were drawn, based on the pressure of gas after complete reaction. The lines obtained were usually very good. They remained straight for 3—4 times as long as the half-life, after which the points were scattered because it was difficult to measure accurately the small changes in pressure; but there was no consistent trend.

Results and Discussion

The results are summarised in the Table. The values for the rate constants at 20° found by Brönsted, Nicholson, and Delbanco [7] are in reasonably good agreement with those found by interpolation from the present work in so far as the bases were common to the two investigations. The present value of k_c for dimethylaniline at 25° fits well on the

Catalytic coefficients, 10 k_c (mole^{-1} kg. min.$^{-1}$) (temp. in parentheses).

Base					$\log_{10} A$	E (kcal. mole^{-1})
p-$C_6H_4Me{\cdot}NEt_2$ ...	377 (8·9°)	1960 (24·5°)	—	19,700 (54·7°)	13·3	14·9
$NPhEt_2$	297 (8·9)	1125 (24·5)	—	10,530 (54·7)	12·7	14·4
p-$C_6H_4Me{\cdot}NMe_2$ ...	124 (9·1)	400 (25·0)	1030 (40·0)	240 (53·0)	10·26	11·77 ± 0·1
$NPhMe_2$	—	168 (25·0)	—	—	12·1 *	14·8 ± 0·4 *
NHPhMe	6·01 (9·1)	24·3 (25·0)	91·5 (40·0)	234 (53·0)	11·69	15·3 ± 0·1
NH_2Ph	1·20 (9·1)	5·43 (25·0)	18·3 (40·0)	45·7 (53·0)	10·76	15·0 ± 0·1
m-$C_6H_4Cl{\cdot}NH_2$ ...	0·198 (9·1)	0·820 (25·0)	2·71 (40·0)	6·68 (53·0)	9·62	14·6 ± 0·1
3,4-$C_6H_3Cl_2{\cdot}NH_2$...	0·070 (8·9)	0·247 (24·5)	—	3·35 (54·7)	9·94	15·6 ± 0·3

* Result of Caldin and Peacock.[3]

In comparing this table with that for the similar quantities in anisole, it should be noted that A factors quoted in ref. 2 are erroneously low by one power of ten.

Arrhenius plot found by Caldin and Peacock. The Arrhenius parameters for all except the first two bases were found by the method of least squares. The errors are probable errors. The same treatment could not be applied to *NN*-diethylaniline or *NN*-diethyl-*p*-toluidine because at the highest temperature k_c for both these bases increased with the base concentration. The value of k_c used in the calculation of the activation energy was for an infinite concentration of base and was found by an extrapolation of the straight line obtained by plotting $1/k$ against $1/[\text{Base}]$. This is an empirical correction with no basis in theory. The Arrhenius parameters obtained in this way are therefore doubtful. It did not seem that the effect could be simply ascribed to the presence of an acidic impurity.

The results of the present work are shown in Fig. 1 in which the activation energies of the catalytic coefficients are plotted against the catalytic coefficients of the various bases at 25°; they are related by the equation:

$$E \text{ (kcal. mole}^{-1}) = 15{\cdot}0 - 0{\cdot}135 \log k_c \text{ (25°) (mole}^{-1} \text{ kg. min.}^{-1})$$

This equation was obtained by the method of least squares, with the values for *NN*-dimethyl-*p*-toluidine omitted. No reason can be suggested for the anomalous behaviour of this base, which was amply confirmed by independent experiments. The equation may be compared with that found for anisole:

$$E \text{ (kcal. mole}^{-1}) = 14{\cdot}2 - 0{\cdot}62 \log k_c \text{ (25°) (mole}^{-1} \text{ kg. sec.}^{-1})$$

This line and the points from which it is derived are also shown in Fig. 1 as is the slope of the line which would be found if variations in log k_c were entirely determined by changes

[7] Brönsted, Nicholson, and Delbanco, *Z. phys. Chem.*, 1934, *A*, **167**, 379.

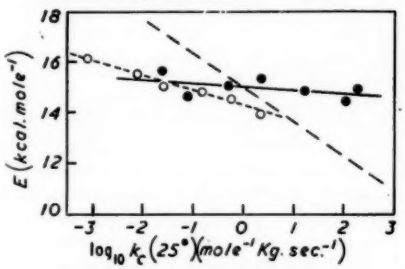
in E, an ideal behaviour which corresponds to a coefficient of log k_c of 1·36. The corresponding equations relating log k_c and A are:

$$m\text{-Cresol: } \log_{10} A \text{ (mole}^{-1} \text{ kg. sec.}^{-1}) = 11{\cdot}0 + 0{\cdot}90 \log k_c \text{ (25°) (mole}^{-1} \text{ kg. sec.}^{-1})$$
$$\text{Anisole: } \log_{10} A \text{ (mole}^{-1} \text{ kg. sec.}^{-1}) = 10{\cdot}4 + 0{\cdot}55 \log_{10} k_c \text{ (25°) (mole}^{-1} \text{ kg. sec.}^{-1})$$

the ideal coefficient of $\log_{10} k_c$ is, of course, zero.

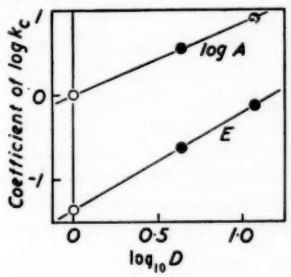
These results confirm, as has been argued by other authors,[3] that the comparison of rate constants measured in different solvents will be misleading because the relation found will depend heavily upon the arbitrarily chosen temperature at which the comparison is made. Clearly it is more satisfactory to compare values of A and E. This was done by Caldin and Peacock [3] for the decomposition of nitramide catalysed by dimethyaniline in nine different solvents. This procedure is little less arbitrary, for whether, for example, $E_{anisole}$ is greater or less than $E_{m\text{-cresol}}$ depends solely upon the base chosen for comparison, as can be seen in Fig. 1. Dimethylaniline is not peculiarly fitted for the purpose.

FIG. 1. *Relation between activation energies and catalytic coefficients for the aniline-catalysed decomposition of nitramide.*



● and solid line: in *m*-cresol.
○ and short dashes: in anisole.
Long dashes: slope = $2{\cdot}303RT$.

FIG. 2. *Relation between the dependence of A and E on* log k_c *and the dielectric constant of the solvent.*



An interesting empirical correlation has been found between the coefficients of log k_c in the expressions for A and E given above and the dielectric constant of the solvent in which the measurements were made. This is shown in Fig. 2. The striking feature of this figure is the fact that the intercepts (corresponding to a solvent of unit dielectric constant) yield coefficients of zero for A and $-1{\cdot}36$ for E. These are the precise values that would be expected if the differences of the catalytic coefficients for different bases were solely due to changes of activation energy, as is postulated in the simple theoretical treatment of free-energy relations. It will not be possible to say for certain whether this finding has any general significance until these reactions in other solvents and also other types of reaction have been studied.

The principal conclusion of this work is that the effect of solvents on reaction velocity cannot usefully be investigated by experiments at one temperature. Even determinations of the activation energies of a single reaction in several solvents are likely to be misleading. Much more work is required on series of related reactions.

THE UNIVERSITY, EDINBURGH.

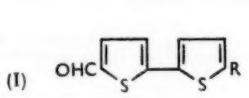
[*Received, April 13th,* 1959.]

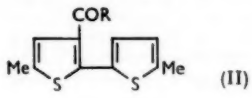
656. *Thiophen Derivatives. Part XIV.*[1] *Some Problems of Substitution in the 2,2′-Bithienyl Series.*

By E. Lescot, jun., Ng. Ph. Buu-Hoï, and N. D. Xuong.

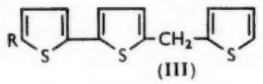
2,2′-Bithienyl is shown to undergo formylation in the 5-position, 5-methyl-2,2′-bithienyl in the 5′-position, and 5,5′-dimethyl-2,2′-bithienyl in the 3-position. 5-(2-Thienylmethyl)-2,2′-bithienyl is formylated in the 5′-position. Numerous new derivatives of 2,2′-bithienyl have been prepared.

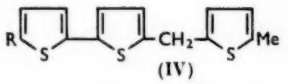
The reactivity of 2,2′-bithienyl has scarcely been investigated. This compound has now been found to react vigorously with dimethylformamide in the presence of phosphorus oxychloride, to give 5-formyl-2,2′-bithienyl (I; R = H); 5-methyl-2,2′-bithienyl, obtained by Wolff–Kishner reduction of this aldehyde, similarly underwent formylation to 5-formyl-5′-methyl-2,2′-bithienyl (I; R = Me). The orientation in both aldehydes was deduced from the fact that reduction of the latter afforded 5,5′-dimethyl-2,2′-bithienyl, which had

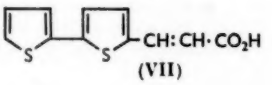


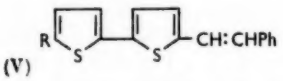


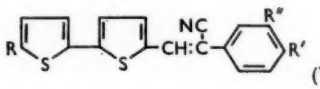
already been prepared by an Ullmann reaction with 2-iodo-5-methylthiophen.[2] In the case of 5,5′-dimethyl-2,2′-bithienyl, formylation occurred in the 3-position, since the resulting aldehyde (II; R = H) was oxidised to an acid identical with that obtained by hypobromite oxidation of 3-acetyl-5,5′-dimethyl-2,2′-bithienyl (II; R = Me); this ketone constituted a by-product in the preparation of the already known 3,3′-diacetyl-5,5′-dimethyl-2,2′-bithienyl.[3] Hypobromite oxidation of the diketone gave 5,5′-dimethyl-2,2′-bithienyl-3,3′-dicarboxylic acid, which readily afforded αα′-dipropyladipic acid on hydrogenolysis with Raney nickel.











An interesting problem of orientation in the same series is offered by formylation of 5-(2-thienylmethyl)-2,2′-bithienyl (III; R = H) [prepared by reduction of 5-(2-thenoyl)-2,2′-bithienyl], experiment showing that the formyl group enters the 5′-position; the aldehyde (III; R = CHO) gave on Wolff–Kishner reduction a compound (III; R = Me) which was different from 5-(5-methyl-2-thienylmethyl)-2,2′-bithienyl (IV), prepared by reduction of 5-(5-methyl-2-thenoyl)-2,2′-bithienyl. These results point to the very high reactivity of the positions 5 and 5′ in the molecule of bithienyl, surpassing even that of the position 5 in a 2-alkylthiophen.

The aldehydes in the 2,2′-bithienyl series were yellow, owing to the high degree of conjugation, but otherwise displayed the general reactive features of aromatic aldehydes; 5-formyl- and 5-formyl-5′-methyl-2,2′-bithienyl, for instance, with benzylmagnesium chloride gave alcohols, which were dehydrated to 5-styryl- (V; R = H) and 5-methyl-5′-styryl-2,2′-bithienyl (V; R = Me) respectively. Like the aldehydes, these highly conjugated molecules were pale yellow. More intensely coloured were the acrylonitriles

[1] Part XIII, Lamy, Lavit, and Buu-Hoï, *J.*, 1958, 4202.
[2] Steinkopf, Leitsmann, Müller, and Wilhelm, *Annalen*, 1939, **541**, 271.
[3] Steinkopf and von Petersdorff, *Annalen*, 1940, **543**, 123.

(VI) prepared by alkali-catalysed condensation of the aldehydes with arylacetonitriles;[4] so also were the chalcones derived by condensation with thiophen ketones. 5-Formyl-2,2′-bithienyl condensed readily with ethyl hydrogen malonate, to give the ethyl ester of the yellow β-(2,2′-bithienyl-5-yl)acrylic acid (VII).

Experimental

5-Formyl-2,2′-bithienyl (I; R = H).—2,2′-Bithienyl (b. p. 129—131°/15 mm.; m. p. 34°) was obtained[5] from 2-iodothiophen and copper powder, along with 2,2′,2″-terthienyl (b. p. 204—210°/0·5 mm.; m. p. 95°) and 2,2′,2″,2‴-quaterthienyl (b. p. 290—315°/0·6 mm.; m. p. 210°). To a mixture of 2,2′-bithienyl (20 g.), dimethylformamide (13·5 g.), and dry toluene (100 c.c.), phosphorus oxychloride (27·6 g.) was added in small portions with stirring, giving rise to an exothermic reaction; after the reaction had subsided, the mixture was heated for 5 hr. on a water-bath and, after cooling, shaken with warm saturated aqueous sodium acetate (200 c.c.). The organic layer was taken up in toluene, the toluene solution was washed with water, dilute aqueous sodium carbonate, and again water, dried (Na_2SO_4), and evaporated under reduced pressure, and the residue was fractionated *in vacuo*. The *aldehyde* (17 g.), b. p. 210°/18 mm., formed pale leaflets, m. p. 59°, from ethanol (Found: C, 55·4; H, 3·0. $C_9H_6OS_2$ requires C, 55·6; H, 3·0%). The *thiosemicarbazone* formed yellow prisms, m. p. 197°, from ethanol (Found: C, 45·0; H, 3·4. $C_{10}H_9N_3S_3$ requires C, 44·7; H, 3·3%); the *4-oxo-Δ²-thiazolin-2-ylhydrazone* formed yellow prisms, m. p. 269°, from ethanol (Found: C, 46·9; H, 3·0. $C_{12}H_9ON_3S_3$ requires C, 46·7; H, 3·1%). Reduction of this aldehyde with hydrazine hydrate and potassium hydroxide in diethylene glycol[6] gave an 80% yield of 5-methyl-2,2′-bithienyl.[7]

β-(2,2′-Bithienyl-5-yl)acrylic Acid (VII).—A solution of the foregoing aldehyde (5 g.) and ethylhydrogen malonate (6 g.) in anhydrous pyridine (50 c.c.) was treated with piperidine (1 c.c.), left for 72 hr., then heated for 1 hr. on a water-bath; most of the pyridine was distilled off *in vacuo*, and water was added to the residue. The product was taken up in ether, and the ethereal solution washed with dilute hydrochloric acid, then with water, dried (Na_2SO_4), and evaporated. The *ethyl ester* (5 g.), b. p. 240°/16 mm., formed pale yellow needles, m. p. 66° (Found: C, 58·9; H, 4·5. $C_{13}H_{12}O_2S_2$ requires C, 59·1; H, 4·6%). The free *acid* obtained on saponification formed yellow prisms, m. p. 177°, from aqueous acetic acid (Found: C, 55·7; H, 3·5. $C_{11}H_8O_2S_2$ requires C, 55·9; H, 3·3%).

5-Styryl-2,2′-bithienyl (V; R = H).—To a Grignard reagent prepared from benzyl chloride (3·6 g.) and magnesium (0·7 g.) in ether (75 c.c.), 5-formyl-2,2′-bithienyl (3 g., in benzene) was added in small portions, and the reaction completed by 15 minutes' heating on a water-bath. After decomposition with cold dilute aqueous sulphuric acid, the ethereal layer was washed with water and dried (Na_2SO_4), and the crude alcohol obtained on evaporation was dehydrated by hot formic acid (5 g.). After cooling and dilution with water, the product was taken up in benzene, washed with water and dried (Na_2SO_4), recovered, and fractionated *in vacuo*. The portion of b. p. 220—240°/0·3 mm. (3 g.) crystallised as yellow needles, m. p. 115° from methanol (Found: C, 71·3; H, 4·4. $C_{16}H_{12}S_2$ requires C, 71·6; H, 4·5%).

5-Formyl-5′-methyl-2,2′-bithienyl (I; R = Me).—Prepared from 5-methyl-2,2′-bithienyl (10 g.), dimethylformamide (7 g.), and phosphorus oxychloride (19 g.) in toluene, this *aldehyde* (9·5 g.), b. p. 208°/18 mm., formed pale yellow prisms, m. p. 98°, from ethanol (Found: C, 57·7; H, 3·8. $C_{10}H_8OS_2$ requires C, 57·6; H, 3·8%). Wolff–Kishner reduction afforded an 80—85% yield of 5,5′-dimethyl-2,2′-bithienyl, m. p. 68° (lit.,[2] m. p. 67°).

5-Methyl-5′-styryl-2,2′-bithienyl (V; R = Me).—Prepared from the appropriate aldehyde (4 g.) and benzylmagnesium chloride, this *compound* (2·5 g.) formed yellow prisms, m. p. 125—126°, from methanol (Found: C, 72·3; H, 5·1. $C_{17}H_{14}S_2$ requires C, 72·3; H, 5·0%).

3-Formyl-5,5′-dimethyl-2,2′-bithienyl (II; R = H).—Obtained from 5,5′-dimethyl-2,2′-bithienyl (8 g.), dimethylformamide (5 g.), and phosphorus oxychloride (7 g.) in toluene, this *compound* (7·5 g.) crystallised as pale yellow leaflets, m. p. 65°, from ethanol (Found: C, 59·8; H, 4·8. $C_{11}H_{10}OS_2$ requires C, 59·5; H, 4·5%).

3-Acetyl-5,5′-dimethyl-2,2′-bithienyl (II; R = Me).—To a solution of 5,5′-dimethyl-2,2′-bithienyl (15 g.) and acetyl chloride (7 g.) in carbon disulphide (75 c.c.), stannic chloride (33·5 g.)

[4] Cf. Buu-Hoï, Hoán, and Lavit, *J.*, 1950, 2130; 1952, 4590.
[5] Cf. Eberhard, *Ber.*, 1894, **27**, 2919; Steinkopf and Roch, *Annalen*, 1930, **482**, 260.
[6] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[7] Steinkopf, Leitsmann, and Hofmann, *Annalen*, 1941, **546**, 180.

XUM

was added in small portions with stirring, and the mixture left for 2 hr. at room temperature, then poured into cold dilute hydrochloric acid; the organic layer was washed with dilute aqueous sodium hydroxide, then with water, dried (Na_2SO_4), the solvent was removed, and the residue fractionated *in vacuo*. The *ketone* (8 g.) formed a pale yellow oil, n_D^{26} 1·6652, which solidified to a crystalline mass, m. p. 49° after recrystallisation from light petroleum (Found: C, 60·7; H, 4·9. $C_{12}H_{12}OS_2$ requires C, 61·0; H, 5·1%). The higher-boiling portion gave, on recrystallisation from ethanol, 3,3′-diacetyl-5,5′-dimethyl-2,2′-bithienyl (3 g.), m. p. 111° (lit.,[3] 111°).

5,5′-Dimethyl-2,2′-bithienyl-3-carboxylic Acid.—To a suspension of 3-formyl-5,5′-dimethyl-2,2′-bithienyl (5 g.) in 1% aqueous sodium hydroxide, a 4% aqueous solution of potassium permanganate (2·3 g.) was added dropwise with stirring, at 5—10°; after 1 hour's stirring, a few drops of sodium hydrogen sulphite were added, the precipitate of manganese oxide was filtered off, and the filtrate acidified with hydrochloric acid. The *acid* which was precipitated formed pale yellow needles (2·5 g.), m. p. 151°, from aqueous acetic acid (Found: C, 55·4; H, 4·2. $C_{11}H_{10}O_2S_2$ requires C, 55·4; H, 4·1%). This acid was identical with the product of oxidation of 3-acetyl-5,5′-dimethyl-2,2′-bithienyl with sodium hypobromite in aqueous dioxan.

5,5′-Dimethyl-2,2′-bithienyl-3,3′-dicarboxylic Acid.—Finely powdered 3,3′-diacetyl-5,5′-dimethyl-2,2′-bithienyl (3 g.) was shaken for 3 hr. with an aqueous solution (50 c.c.) of sodium hypobromite prepared from bromine (2·3 c.c.) and sodium hydroxide (4·1 g.); the bromoform was decanted off, and the aqueous layer treated with sodium hydrogen sulphite and acidified with hydrochloric acid. The *diacid* which was precipitated formed yellowish prisms (2 g.), m. p. 296—298°, from aqueous acetic acid (Found: C, 50·7; H, 3·7. $C_{12}H_{10}O_4S_2$ requires C, 51·0; H, 3·5%).

αα-Dipropyladipic Acid.[8]—To a solution of the above diacid (3 g.) in 10% aqueous sodium hydroxide (300 c.c.), Raney nickel (60 g.) was added portionwise with stirring, stirring was continued, and the mixture heated on a water-bath for 2 hr. The precipitated nickel was filtered off and washed with water, and the cooled filtrate was acidified with hydrochloric acid. The organic *acid* was taken up in ether, washed with water, and dried (Na_2SO_4); the residue left on evaporation of the solvent formed colourless prisms, m. p. 100—101°, from light petroleum (Found: C, 58·3; H, 9·5. $C_{12}H_{22}O_4,H_2O$ requires C, 58·0; H, 9·6%).

5-(2-*Thenoyl*)-2,2′-*bithienyl*.—To a solution of 2,2′-bithienyl (12 g.) and 2-thenoyl chloride (13·2 g.) in carbon disulphide (75 c.c.), stannic chloride (32·5 g.) was added portionwise with stirring, and the mixture left for 2 hr. at room temperature, then worked up in the usual way. The *ketone* (10 g.), b. p. 265—270°/18 mm., formed yellow needles, m. p. 104° (from ethanol) (Found: C, 56·7; H, 3·0. $C_{13}H_8OS_3$ requires C, 56·5; H, 2·9%).

5-(2-*Thienylmethyl*)-2,2′-*bithienyl* (III; R = H).—A solution of the foregoing compound (5 g.) and 95% hydrazine hydrate (5 g.) in diethylene glycol (30 c.c.) was briefly refluxed to allow the hydrazone to form, and, after cooling, potassium hydroxide (5 g.) was added; the mixture was then refluxed for 2 hr. with removal of water and, when cool, acidified with dilute hydrochloric acid. The *product* was taken up in benzene, washed with water, dried ($CaCl_2$), recovered, and fractionated *in vacuo*. The portion (3·5 g.), b. p. 225—228°/15 mm., n_D^{27} 1·6991, formed colourless needles, m. p. 46°, from ethanol (Found: C, 59·7; H, 4·1. $C_{13}H_{10}S_3$ requires C, 59·5; H, 3·8%).

5-*Formyl*-5′-(2-*thienylmethyl*)-2,2′-*bithienyl* (III; R = CHO).—Prepared in the usual way from the foregoing compound (6 g.), dimethylformamide (2·5 g.), and phosphorus oxychloride (5·3 g.) in toluene (50 c.c.), this *aldehyde* (5·2 g.), b. p. 265—268°/17 mm., formed yellow prisms, m. p. 109°, from ethanol (Found: C, 57·9; H, 3·5. $C_{14}H_{10}OS_3$ requires C, 57·9; H, 3·5%).

5-*Methyl*-5′-(2-*thienylmethyl*)-2,2′-*bithienyl* (III; R = Me).—Prepared by reduction of the preceding aldehyde (1·7 g.) with hydrazine hydrate (1·7 g.) and potassium hydroxide (1·7 g.) in diethylene glycol (15 c.c.), this *compound* (1 g.) crystallised as colourless leaflets, m. p. 42°, from light petroleum (Found: C, 60·8; H, 4·2. $C_{14}H_{12}S_3$ requires C, 60·9; H, 4·4%).

5-(5-*Methyl*-2-*thenoyl*)-2,2′-*bithienyl*.—Prepared from 2,2′-bithienyl (8 g.), 5-methyl-2-thenoyl chloride (8 g.), and stannic chloride (25 g.) in carbon disulphide, this *ketone* (7 g.), b. p. 289—290°/18 mm., formed yellow needles, m. p. 103°, from ethanol (Found: C, 57·8; H, 3·4. $C_{14}H_{10}OS_3$ requires C, 57·9; H, 3·5%).

5-(5-*Methyl*-2-*thienylmethyl*)-2,2′-*bithienyl* (IV; R = H).—Obtained by reduction of the

[8] For similar hydrogenolysis of thiophen compounds to aliphatic diacids, see Buu-Hoï, Sy, and Xuong, *Compt. rend.*, 1955, **240**, 442.

foregoing compound (2·5 g.) with hydrazine hydrate (2·5 g.) and potassium hydroxide (2·5 g.) in diethylene glycol (15 c.c.), this *compound* (2 g.), b. p. 243—245°/15 mm., n_D^{25} 1·6857, formed colourless leaflets, m. p. 44°, from light petroleum (Found: C, 60·8; H, 4·3%).

β-(2,2′-*Bithienyl-5-yl*)-α-*phenylacrylonitrile* (VI; R = R′ = R″ = H).—To a solution of 5-formyl-2,2′-bithienyl (0·2 g.) and phenylacetonitrile (0·2 g.) in ethanol, a few drops of 25% aqueous sodium hydroxide were added with stirring, producing immediately a precipitate of the *nitrile*, which was collected, washed with water, and recrystallised from acetone as orange-yellow leaflets (2 g.), m. p. 147°, giving a red halochromy in sulphuric acid (Found: C, 69·7; H, 3·5. $C_{17}H_{11}NS_2$ requires C, 69·6; H, 3·8%).

α-p-*Chlorophenyl*-β-(2,2′-*bithienyl-5-yl*)*acrylonitrile* (VI; R = R″ = H; R′ = Cl), prepared from *p*-chlorophenylacetonitrile, formed orange-yellow leaflets, m. p. 204° (from acetone) (Found: C, 62·6; H, 3·2. $C_{17}H_{10}NS_2Cl$ requires C, 62·3; H, 3·1%); β-(2,2′-*bithienyl-5-yl*)-α-(3,4-*dichlorophenyl*)*acrylonitrile* (VI; R = H; R′ = R″ = Cl) formed orange-yellow needles, m. p. 223° (from acetone) (Found: C, 56·5; H, 2·5. $C_{17}H_9NS_2Cl_2$ requires C, 56·4; H, 2·5%); α-p-*chlorophenyl*-β-(5′-*methyl*-2,2′-*bithienyl-5-yl*)*acrylonitrile* (VI; R = Me; R′ = Cl; R″ = H), similarly prepared from the aldehyde (I; R = Me), formed orange leaflets, m. p. 189°, from acetone, giving a violet halochromy in sulphuric acid (Found: C, 63·0; H, 3·6. $C_{18}H_{12}NS_2Cl$ requires C, 63·3; H, 3·5%).

α-(2,2′-*Bithienyl-5-yl*)-β-(5-*chloro*-2-*thenoyl*)*ethylene*.—Prepared by shaking a solution of 5-formyl-2,2′-bithienyl (0·2 g.) and 2-acetyl-5-chlorothiophen (0·2 g.) in ethanol with a few drops of 20% aqueous sodium hydroxide, this *ketone* formed deep yellow needles, m. p. 120°, from ethanol, giving a brown-red halochromy in sulphuric acid (Found: C, 53·7; H, 2·9. $C_{15}H_9OS_3Cl$ requires C, 53·5; H, 2·7%); β-(5-*chloro*-2-*thenoyl*)-α-(5,5′-*dimethyl*-2,2′-*bithienyl*-3-*yl*)*ethylene*, similarly prepared from the aldehyde (II; R = H), formed deep yellow needles, m. p. 136° (from ethanol), giving a violet halochromy in sulphuric acid (Found: C, 55·6; H, 3·7. $C_{17}H_{13}OS_3Cl$ requires C, 55·9; H, 3·6%).

THE RADIUM INSTITUTE, THE UNIVERSITY OF PARIS. [*Received, April 6th*, 1959.]

---

657. *Cyclodehydration of Arylidene-α-tetralones derived from Fluorene, Dibenzofuran, and Dibenzothiophen.*

By G. SAINT-RUF, NG. PH. BUU-HOÏ, and P. JACQUIGNON.

Arylidene-α-tetralones derived from fluorene, dibenzofuran, and dibenzothiophen undergo cyclodehydration to polycyclic compounds when treated with phosphorus pentoxide. Some similar condensed carbazoles have also been prepared.

CYCLODEHYDRATION of 2-benzylidene-α-tetralone to 3,4-benzofluorene under the influence of phosphorus pentoxide [1] has been used for the synthesis of a large number of condensed fluorene hydrocarbons.[2] It has now been extended to arylidene derivatives of 6,7,8,9-tetrahydro-6-oxo-11*H*-benzo[*b*]fluorene (I), a ketone readily prepared from fluorene by the succinic anhydride method.[3] This ketone underwent alkali-catalysed condensation with benzaldehyde and 1-naphthaldehyde, to the corresponding arylidene compounds which were cyclodehydrated in the presence of phosphoric oxide to fluoreno[3,4-*b*]fluorene (II) and benzo[*a*]fluoreno[3,2-*g*]fluorene (III). A heterocyclic analogue was prepared by indolisation of the phenylhydrazone of ketone (I) and dehydrogenation, with chloranil, to fluoreno-[2,3-*c*]carbazole (IV).

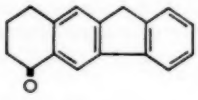
Oxygen- and sulphur-containing heterocyclic analogues of the ketone (I) are accessible from dibenzofuran [4] and dibenzothiophen,[5] and the cyclodehydration of arylidene derivatives of the ketones (V) and (VI) afforded compounds (VII) and (VIII); similarly, the

[1] Rapson and Shuttleworth, *J.*, 1940, 536.
[2] Buu-Hoï and Cagniant, *Rev. sci.*, 1942, **80**, 319, 384; 1943, **81**, 30; Cagniant, *Compt. rend.*, 1948, **226**, 137; *Bull. Soc. chim. France*, 1949, 382; Buu-Hoï and Saint-Ruf, *J.*, 1957, 3806.
[3] Barnett, Goodway, and Watson, *Ber.*, 1933, **66**, 1876.
[4] Mosettig and Robinson, *J. Amer. Chem. Soc.*, 1935, **97**, 902.
[5] Gilman and Jacoby, *J. Org. Chem.*, 1938, **3**, 108; Buu-Hoï and Cagniant, *Ber.*, 1943, **76**, 1269.

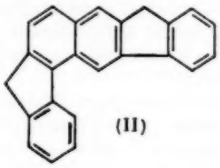
XUM

α-naphthylidene and the 5-acenaphthylidene derivatives of ketone (VI) could be cyclodehydrated to the polycyclic compounds (IX) and (X).

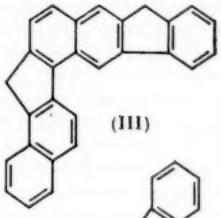
A related route to condensed thiophen derivatives is the condensation of 3-formylthionaphthen with polycyclic tetralones, and cyclodehydration of the resulting unsaturated



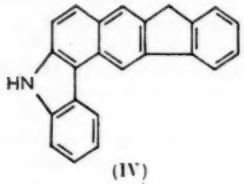
(I)



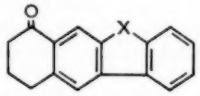
(II)



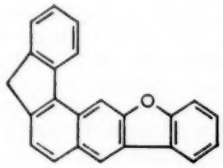
(III)



(IV)



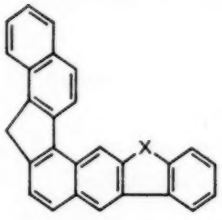
(V) X = O
(VI) X = S



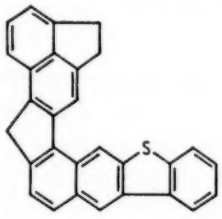
(VII)

ketones. For instance, 3-formylthionaphthen [6] gave with 7,8,9,10-tetrahydro-7-oxobenzo[*a*]pyrene the ketone (XI), which was easily cyclised to the yellow octacyclic compound (XII).

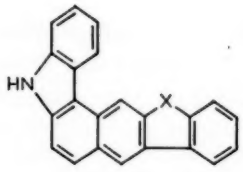
As in the case of the fluorene ketone (I), the furan and thiophen derivatives (V) and



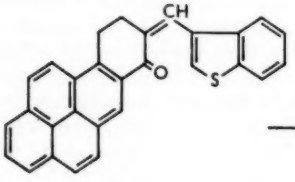
(VIII) X = O
(IX) X = S



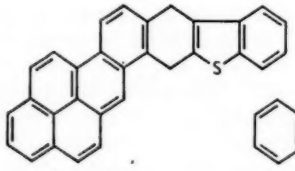
(X)



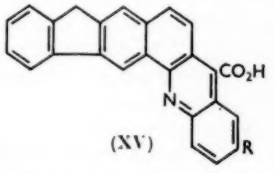
(XIII) X = O
(XIV) X = S



(XI)



(XII)



(XV)

(VI) readily gave the condensed carbazoles, (XIII) and (XIV), which gave coloured 1 : 1 molecular complexes [8] with tetrachloro- and tetrabromo-phthalic anhydride. Pfitzinger reaction of ketone (I) with isatin and 5-bromoisatin led to the polycyclic cinchoninic acids

[6] Cf. King and Nord, *J. Org. Chem.*, 1948, **13**, 635; Buu-Hoï and Hoán, *J.*, 1951, 251.
[7] Saint-Ruf, Buu-Hoï, and Jacquignon, *J.*, 1948, 48.
[8] Buu-Hoï and Jacquignon, *Compt. rend.*, 1952, **234**, 1056; *Bull. Soc. chim. France*, 1957, 488.

(XV; R = H or Br); decarboxylation of the non-halogenated compound yielded 7,8-dihydro-5*H*-fluoreno[2,3-*c*]acridine.

Experimental

Preparation of Ketone (I).—As an improvement on the Koelsch procedure,[9] β-2-fluorenoylpropionic acid was prepared in 87% yield by adding aluminium chloride (55 g.) to an ice-cooled mixture of fluorene (60 g.), succinic anhydride (44 g.), and nitrobenzene (200 c.c.); after 36 hr. at room temperature, the mixture was worked up in the usual way, giving a product (90 g.), m. p. 212—213° (from acetic acid). This keto-acid was best reduced by the Wolff–Kishner method, using Huang-Minlon's technique, and the chloride of the resulting γ-2-fluorenylbutyric acid was cyclised with aluminium chloride in benzene, to ketone (I), b. p. 257—258°/15 mm. (60% yield).

7-*Benzylidene*-6,7,8,9-*tetrahydro*-6-*oxo*-11H-*benzo*[b]*fluorene*.—An ethanolic solution of the above ketone (3 g.) and benzaldehyde (1·4 g.) was shaken with 4% alcoholic potassium hydroxide (50 c.c.) and left for 3 hr. in the refrigerator. The solid *derivative* was then collected, washed with dilute aqueous acetic acid and with water, and recrystallised from ethanol as yellow needles (3 g.), m. p. 153°, giving a deep red halochromy in sulphuric acid (Found: C, 89·4; H, 5·5. $C_{24}H_{18}O$ requires C, 89·4; H, 5·6%).

Fluoreno[3,4-b]*fluorene* (II).—A solution of the foregoing chalcone (2 g.) in dry xylene (75 c.c.) was refluxed with phosphoric oxide (1·75 g.) for 30 hr.; the hot liquid was filtered off, and the filtrate washed with aqueous sodium hydroxide, then with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was treated with picric acid in ethanol, and the brown picrate (m. p. 99°) was decomposed with aqueous ammonia, giving the *hydrocarbon* (5%), yellowish needles, m. p. 259° (from ethanol–benzene) (Found: C, 94·4; H, 5·4. $C_{24}H_{16}$ requires C, 94·7; H, 5·3%).

6,7,8,9-*Tetrahydro*-7-1′-*naphthylidene*-6-*oxo*-11H-*benzo*[b]*fluorene*.—Prepared from ketone (I) (3 g.) and 1-naphthaldehyde (2 g.) in the usual way, this *ketone* formed yellow prisms (3 g.), m. p. 164—165°, from ethanol–benzene, giving a violet halochromy with sulphuric acid (Found: C, 90·1; H, 5·4. $C_{28}H_{20}O$ requires C, 90·3; H, 5·4%).

Benzo[a]*fluoreno*[3,2-g]*fluorene* (III).—Cyclodehydration of the foregoing chalcone (2·5 g.) with phosphoric oxide (2 g.) afforded a 4% yield of *hydrocarbon*, yellowish needles, m. p. 275° (from ethanol–benzene) (Found: C, 94·9; H, 5·2. $C_{28}H_{18}$ requires C, 94·9; H, 5·1%).

5,6,7,9-*Tetrahydrofluoreno*[2,3-c]*carbazole*.—A mixture of ketone (I) (1·5 g.) and phenylhydrazine (1 g.) was heated at 120° until steam ceased to be evolved; after cooling, acetic acid saturated with hydrogen chloride (20 c.c.) was added to the crude phenylhydrazone, and the mixture brought to the b. p., then poured in water. The precipitated *carbazole* separating on cooling recrystallised from ethanol as cream-coloured needles (1·7 g.), m. p. 224°, giving a yellow halochromy in sulphuric acid (Found: C, 89·6; H, 5·8. $C_{23}H_{17}N$ requires C, 89·9; H, 5·5%); the *picrate* formed dark violet needles, m. p. 186—187°, from ethanol (Found: N, 10·6. $C_{29}H_{20}O_7N_4$ requires N, 10·4%). This tetrahydrocarbazole gave with tetrachlorophthalic anhydride a red complex, m. p. 238° (decomp.), in acetic acid, and with tetrabromophthalic anhydride, a red complex, m. p. 249—250°.

Fluoreno[2,3-c]*carbazole* (IV).—The tetrahydrocarbazole (1 g.) in dry xylene (50 c.c.) was refluxed with chloranil (2 g.) for 3 hr. The hot liquid was filtered, the filtrate washed first with 15% aqueous sodium hydroxide, then with water, and dried (Na_2SO_4), and the solvent was distilled off *in vacuo*. The residual *base* formed colourless needles (0·5 g.), m. p. >340°, from ethanol–benzene (Found: C, 90·2; H, 4·7; N, 4·7. $C_{23}H_{15}N$ requires C, 90·5; H, 4·9; N, 4·6%).

8-*Benzylidene*-7,8,9,10-*tetrahydro*-7-*oxobenzo*[b]*naphtho*[2,3-d]*furan*.—Ketone (V) was prepared from dibenzofuran and succinic anhydride according to Mosettig and Robinson's directions,[4] except that the intermediary keto-acid was reduced by Wolf–Kishner–Huang-Minlon's method. Condensing this ketone (3 g.) with benzaldehyde (1·4 g.) gave a *benzylidene derivative* (4 g.), yellowish needles, m. p. 205° (from ethanol), giving a deep red halochromy in sulphuric acid (Found: C, 85·2; H, 5·0. $C_{23}H_{16}O_2$ requires C, 85·2; H, 4·9%).

Fluoreno[3,4-b]*dibenzofuran* (VII).—Cyclodehydration of the foregoing derivative afforded a 7% yield of a *compound*, crystallising as cream-coloured needles, m. p. 221°, from ethanol (Found: C, 90·2; H, 4·6. $C_{23}H_{14}O$ requires C, 90·2; H, 4·6%).

[9] Koelsch, *J. Amer. Chem. Soc.*, 1933, **55**, 3885.

XUM

7,8,9,10-*Tetrahydro*-8-α-*naphthylidene*-7-*oxobenzo*[b]*naphtho*[2,3-d]*furan*.—Prepared from ketone (V) and 1-naphthaldehyde, this *derivative* formed pale yellow prisms, m. p. 225°, from ethanol–benzene, giving a violet halochromy in sulphuric acid (Found: C, 86·8; H, 4·9. $C_{37}H_{18}O_2$ requires C, 86·6; H, 4·8%).

Benzo[7,8]*fluoreno*[2,1-b]*dibenzofuran* (VIII).—Prepared from the above chalcone, this *compound* formed cream-coloured needles, m. p. 278°, from ethanol–benzene (Found: C, 91·3; H, 4·5. $C_{27}H_{16}O$ requires C, 91·0; H, 4·5%).

5,6-*Dihydro*(*dibenzofurano*)[2,3-c]*carbazole*.—Obtained from ketone (V) (1·5 g.) and phenylhydrazine (1 g.), this *compound* formed colourless needles (1·7 g.), m. p. 251—252°, from ethanol, giving a lemon-yellow halochromy in sulphuric acid (Found: C, 85·5; H, 4·9; N, 4·3. $C_{32}H_{19}ON$ requires C, 85·4; H, 4·9; N, 4·5%). The *picrate* formed violet needles, m. p. 210° (from ethanol) (Found: N, 10·3. $C_{38}H_{22}O_8N_4$ requires N, 10·4%); the *addition compound* with tetrachlorophthalic anhydride formed cherry-red needles, m. p. 234—235° (decomp. >212°), from acetic acid (Found: C, 60·4; H, 2·5. $C_{30}H_{15}O_4NCl_4$ requires C, 60·5; H, 2·5%).

(*Dibenzofurano*)[2,3-c]*carbazole* (XIII).—Obtained by dehydrogenation of the foregoing product (1 g.) with chloranil (1·6 g.), this *carbazole* formed colourless prisms, m. p. >340° (from ethanol–benzene), giving an orange halochromy in sulphuric acid (Found: C, 86·1; H, 4·2. $C_{32}H_{19}ON$ requires C, 86·0; H, 4·2%). The *picrate* formed violet needles, m. p. 218—219° (from ethanol–benzene) (Found: N, 10·5. $C_{38}H_{22}O_8N_4$ requires N, 10·4%); the orange addition compound with tetrachlorophthalic anhydride melted at 245° (decomp. >206°).

7,8,9,10-*Tetrahydro*-8-α-*naphthylidene*-7-*oxobenzo*[b]*naphtho*[2,3-d]*thiophen*.—Ketone (VI) was prepared from dibenzothiophen and succinic anhydride,[5] the intermediary keto-acid being reduced, in 94% yield, by the Huang-Minlon technique. Condensing this ketone (3·5 g.) with 1-naphthaldehyde (2·5 g.) afforded a *derivative*, crystallising as pale yellow prisms (5 g.), m. p. 197°, from ethanol–benzene, and giving a violet halochromy in sulphuric acid (Found: C, 83·0; H, 4·5. $C_{27}H_{18}OS$ requires C, 83·1; H, 4·6%).

Benzo[7,8]*fluoreno*[2,1-b]*dibenzofuran* (IX).—Cyclodehydration of the foregoing ketone afforded a *compound*, crystallising as colourless needles, m. p. 289° (decomp.), from ethanol–benzene (Found: C, 87·0; H, 4·2. $C_{27}H_{16}S$ requires C, 87·1; H, 4·3%).

8-5′-*Acenaphthylidene*-7,8,9,10-*tetrahydro*-7-*oxobenzo*[b]*naphtho*[2,3-d]*thiophen*.—Prepared from ketone (VI) (3 g.) and 5-acenaphthaldehyde (2·5 g.), this *chalcone* (4 g.) formed yellow prisms, m. p. 238° (from ethanol–benzene), giving a violet halochromy in sulphuric acid (Found: C, 83·6; H, 5·1. $C_{29}H_{20}OS$ requires C, 83·7; H, 4·8%). Cyclodehydration furnished 15,16-*dihydro*-4H-*acenaphthyleno*[5′,4′:2,3]*indeno*[4,5-b]*dibenzothiophen* (X), yellowish needles, m. p. 264°, from ethanol–benzene (Found: C, 87·5; H, 4·6. $C_{29}H_{18}S$ requires C, 87·4; H, 4·5%).

7,8,9,10-*Tetrahydro*-7-*oxo*-8-(3-*thionaphthylmethylene*)[a]*pyrene* (XI).—This *derivative*, prepared by condensation of 3-formylthionaphthen (3·5 g.) with 7,8,9,10-tetrahydro-7-oxobenzo[*a*]pyrene (5·8 g.), crystallised as deep yellow prisms (6 g.), m. p. 262°, from ethanol–benzene (Found: C, 84·0; H, 4·3. $C_{29}H_{18}OS$ requires C, 84·1; H, 4·3%).

Pyreno[1′,2′:6,7]*indeno*[1,2-*b*]*thionaphthen* (XII).—Obtained from the foregoing derivative (5 g.), this *compound* formed yellow prisms (0·25 g.), m. p. 276°, from ethanol–benzene (Found: C, 87·9; H, 4·0. $C_{29}H_{16}S$ requires C, 87·9; H, 4·0%) (picrate, brown-red needles from ethanol).

8-*Benzylidene*-7,8,9,10-*tetrahydro*-7-*oxobenzo*[b]*naphtho*[2,3-d]*thiophen*.—Prepared from ketone (VI) (3·5 g.) and benzaldehyde (1·5 g.), this *compound* (4 g.) formed pale yellow prisms, m. p. 181—182°, from ethanol–benzene, giving an orange-red halochromy in sulphuric acid (Found: C, 81·0; H, 4·7. $C_{23}H_{16}OS$ requires C, 81·2; H, 4·7%). Cyclodehydration of this ketone afforded a compound, m. p. 187°.

8-5′-*Acenaphthylidene*-7,8,9,10-*tetrahydro*-7-*oxobenzo*[b]*naphtho*[2,3-d]*furan*.— Prepared from ketone (V) (2 g.) and 5-acenaphthaldehyde (1·5 g.), this *derivative* (2·6 g.) formed orange prisms, m. p. 209°, from ethanol–benzene, giving a brown-violet halochromy in sulphuric acid (Found: C, 87·2; H, 4·9. $C_{29}H_{20}O_2$ requires C, 87·0; H, 5·0%).

5,6-*Dihydro*(*dibenzothieno*)[2,3-c]*carbazole*.—This *compound*, prepared from ketone (VI) (1·5 g.) and phenylhydrazine (1 g.), formed colourless prisms (2 g.), m. p. 282—283°, from ethanol (yellow halochromy in sulphuric acid) (Found: C, 81·2; H, 4·6. $C_{32}H_{19}NS$ requires C, 81·2; H, 4·6%) [*picrate*, violet needles, m. p. 193° (from ethanol) (Found: N, 10·0. $C_{38}H_{22}O_7N_4S$ requires N, 10·0%)]. The addition compound with tetrachlorophthalic anhydride was red, and that with tetrabromophthalic anhydride was vermilion.

Dibenzothieno[2,3-c]*carbazole* (XIV).—Prepared by dehydrogenation of the foregoing compound, this *carbazole* formed yellowish prisms, m. p. >340°, from ethanol (Found: C, 81·6; H, 4·1. $C_{22}H_{13}NS$ requires C, 81·7; H, 4·0%) (picrate, violet needles, m. p. 207°, from ethanol).

7,8-*Dihydro*-5H-*fluoreno*[2,3-c]*acridine*-9-*carboxylic Acid* (XV; R = H).—A mixture of ketone (I) (2·5 g.), isatin (1·7 g.), and a 20% solution (50 c.c.) of potassium hydroxide in ethanol was refluxed for 18 hr.; after evaporation, the solid was washed with ether and acidified with aqueous acetic acid. The *cinchoninic acid* recrystallised from ethanol as yellowish prisms (2 g.), m. p. >350° (Found: C, 82·3; H, 4·4; N, 4·1. $C_{25}H_{17}O_2N$ requires C, 82·6; H, 4·7; N, 3·9%). Thermal decarboxylation of this acid afforded the *acridine* (XV; R = H), yellowish needles, m. p. 174° (from ethanol–benzene) (Found: N, 4·4. $C_{24}H_{17}N$ requires N, 4·4%) [*picrate*, orange needles, m. p. 234—235° (from ethanol–benzene) (Found: N, 10·0. $C_{30}H_{20}O_7N_4$ requires N, 10·2%)].

11-*Bromo*-7,8-*dihydrofluoreno*[2,3-c]*acridine*-9-*carboxylic Acid* (XV; R = Br).—Prepared as for the above from ketone (I) and 5-bromoisatin, this *acid* formed yellow needles, m. p. 335°, from ethanol–benzene (Found: N, 3·0; Br, 17·8. $C_{25}H_{16}O_2NBr$ requires N, 3·2; Br, 18·1%).

This work was done under a grant from the Service d'Exploitation Industrielle des Tabacs et des Allumettes, for which our thanks are due to Dr. J. Cuzin, Scientific Director.

THE RADIUM INSTITUTE, THE UNIVERSITY OF PARIS. [*Received, April 21st,* 1959.]

---

658. *The π-Electronic Structure and Properties of Naphthalene.*

By T. E. PEACOCK.

The "atom" and "bond" populations in naphthalene are calculated. By using different atomic orbital bases the values of the oscillator strengths for the first four singlet excited states are calculated.

VARIOUS authors have recently applied Roothaan's self-consistent field (SCF) method,[1] as modified for π-electron molecules,[2] to a calculation of the structure and properties of naphthalene.[2-5] Pariser [6] published a configuration interaction calculation in which a large number of the singly excited configurations were used. The most satisfactory simplification for the various assumptions involved [2,6] seems to depend on the use of a suitable basis of orthogonalized atomic orbitals, in which case the integrals which are neglected are indeed very small.[7-9] In this paper the SCF bond orders which were calculated on such a basis [4] are transformed into those which occur in the basis of ordinary carbon $2p_z$ atomic orbitals, and are compared with those of an earlier calculation.[10] The values of the oscillator strengths for the first four singlet transitions using the two atomic orbital bases are compared.

Charge Distribution.—The bond orders in the orthogonal atomic orbital basis [11] have been reported previously.[4] These atomic orbitals are neither well localized nor centrosymmetric,[10-12] and therefore the $\bar{P}_{ij}$ which represent the "formal" charges ($i = j$) and bond orders ($i \neq j$) do not give a direct description of the charge distribution in the molecule.

[1] Roothaan, *Rev. Mod. Phys.*, 1955, **23**, 69.
[2] Pople, *Trans. Faraday Soc.*, 1953, **49**, 1375.
[3] Moser and Brion, *J. Chim. phys.*, 1955, **52**, 25; Lefebvre and Moser, *J.*, 1956, 1557, 2743; Pople, *Proc. Phys. Soc.*, 1955, **68**, *A*, 81.
[4] Peacock, *Trans. Faraday Soc.*, 1957, **53**, 1042.
[5] Peacock, *Proc. Phys. Soc.*, 1957, **70**, *A*, 654.
[6] Pariser, *J. Chem. Phys.*, 1956, **24**, 250.
[7] McWeeny, *Proc. Roy. Soc.*, 1955, *A*, **227**, 288.
[8] *Idem, ibid.*, 1956, *A*, **237**, 355.
[9] Hall, *Trans. Faraday Soc.*, 1954, **50**, 773.
[10] McWeeny, *J. Chem. Phys.*, 1951, **19**, 1614.
[11] Lowdin, *ibid.*, 1950, **18**, 365.
[12] McWeeny, *Proc. Roy. Soc.*, 1955, *A*, **232**, 114.

If $\mathbf{a}$ is the row matrix $(a_1, a_2, \ldots a_n)$ of $2p$ atomic orbitals and $\bar{a}$ is that of the orthonormalized $2p$ atomic orbitals, then:[11]

$$\bar{\mathbf{a}} = \mathbf{a}\,\mathbf{S}^{-\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $\mathbf{S}$ is the matrix of overlap integrals.

Let $\overline{\mathbf{T}}$ be an $m \times n$ matrix whose n columns represent the coefficients of the m orthonormal orbitals in the n molecular orbitals.[9] Then $\overline{\mathbf{A}} = (ABC) = \overline{\mathbf{a}}\overline{\mathbf{T}}$, and the one electron density is

$$P(1) = \sum_{ij} \bar{a}_i(1)\,\overline{P}_{ij}\bar{a}_j^*(1)$$

where $\overline{\mathbf{P}} = 2\overline{\mathbf{T}}\overline{\mathbf{T}}^{\dagger}$ is the density matrix.

If expression (1) is used, alternative expressions are $\mathbf{A} = \mathbf{a}\mathbf{T}$ where $\mathbf{T} = \mathbf{S}^{-\frac{1}{2}}\overline{\mathbf{T}}$ and

$$P(1) = \sum_{ij} a_i(1)P_{ij}a_j^*(1)$$

where $\mathbf{P} = 2\mathbf{T}\mathbf{T}^{\dagger} = \mathbf{S}^{-\frac{1}{2}}\overline{\mathbf{P}}\mathbf{S}^{-\frac{1}{2}}$. $\mathbf{P}$ is the density matrix in the non-orthogonal basis of ordinary $2p$-orbitals, its elements indicating the charges in well-defined regions.

The amounts of charge assigned to the orbital (atom) and overlap (bond) regions are then (by integration)

$$q_{ii} = P_{ii}$$

and $$q_{ij} = 2P_{ij}S_{ij} \text{ (real orbitals being assumed)}$$

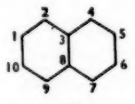
and $$tr\mathbf{PS} = N \text{ (the total number of } \pi\text{-electrons)}$$

These are the orbital and overlap " populations " [13] or " atom " and " bond charges." [10]

Application to Naphthalene.—The numbering used here for naphthalene is given in (I). The values of the overlap integrals are given in Table 1.

TABLE 1.

S_{12}	S_{13}	S_{14}	S_{15}	S_{16}	S_{17}	S_{18}
0·260	0·039	0·002	0·000	0·000	0·001	0·018



(I)

The matrix $\mathbf{S}^{-\frac{1}{2}}$ was computed by rewriting $\mathbf{S}$ as $(\mathbf{1} + \mathbf{x})$ and expanding as a matrix power series, six terms giving adequate accuracy.

The π-charge distribution in naphthalene is given in Table 2 and compared with that of McWeeny [10] who set all overlap integrals except S_{12} equal to zero. The values of P_{ij} and $\overline{P}_{ij}$ are also given

TABLE 2.

	11	12	22	23	33	38	1,10
q	0·759	0·300	0·772	0·177	0·737	0·211	0·200
q [10]	0·757	0·273	0·767	0·193	0·719	0·178	0·213
P	0·759	0·567	0·772	0·341	0·737	0·405	0·382
$\overline{P}$ [4]	1·000	0·754	1·000	0·526	1·000	0·576	0·572

It is seen that each atom has a deficiency of π-electrons and therefore a net positive charge of about 0·2 electron unit while each bond contains a net negative charge of about 0·2.

The Excited States of Naphthalene.—The energies of the excited states predicted by using limited configuration interaction have already been published and discussed.[5] The wave functions for the excited states together with their energies relative to the ground state are given below, B, A, A', and B' being the two highest occupied and two lowest unoccupied orbitals in ascending energy order,

[13] Mulliken, *J. Chem. Phys.*, 1955, **23**, 1833.

TABLE 3.

$$\Psi'_p = 0{\cdot}9345\Phi(A \longrightarrow A') + 0{\cdot}3561\Phi(B \longrightarrow B') \qquad E_p = 4{\cdot}54 \text{ ev}$$
$$\Psi'_\alpha = 0{\cdot}7071\Phi(A \longrightarrow B') - 0{\cdot}7071\Phi(B \longrightarrow A') \qquad E_\alpha = 4{\cdot}45 \text{ ev}$$
$$\Psi'_\beta = 0{\cdot}7071\Phi(A \longrightarrow B') + 0{\cdot}7071\Phi(B \longrightarrow A') \qquad E_\beta = 6{\cdot}34 \text{ ev}$$
$$\Psi'_{\beta'} = 0{\cdot}3561\Phi(A \longrightarrow A') - 0{\cdot}9345\Phi(\mathrm{B} \longrightarrow \mathrm{B}') \qquad E_{\beta'} = 6{\cdot}65 \text{ ev}$$

where for example $\Phi(B \longrightarrow B')$ is the wave function of the configuration in which one electron has been excited from molecular orbital B to B'.

The relevant SCF molecular orbitals (in the orthogonal basis) are given in Table 4.

TABLE 4.

$$\psi_B = 0{\cdot}3950\ (\bar{a}_1 + \bar{a}_5 + \bar{a}_6 + \bar{a}_{10}) - 0{\cdot}4336\ (\bar{a}_3 + \bar{a}_8)$$
$$\psi_A = 0{\cdot}2643\ (\bar{a}_1 - \bar{a}_5 + \bar{a}_6 - \bar{a}_{10}) + 0{\cdot}4145\ (\bar{a}_2 - \bar{a}_4 + \bar{a}_7 - \bar{a}_9)$$
$$\psi_{A'} = 0{\cdot}2643\ (\bar{a}_1 - \bar{a}_5 - \bar{a}_6 + \bar{a}_{10}) - 0{\cdot}4145\ (\bar{a}_2 - \bar{a}_4 - \bar{a}_7 + \bar{a}_9)$$
$$\psi_{B'} = 0{\cdot}3950\ (\bar{a}_1 + \bar{a}_5 - \bar{a}_6 - \bar{a}_{10}) - 0{\cdot}4336\ (\bar{a}_3 - \bar{a}_8)$$

The oscillator strength for a transition $\Psi'_\alpha \longrightarrow \Psi'_\beta$ is given [14] by

$$f_{\alpha\beta} = 1{\cdot}085 \times 10^{11}\, \bar{\nu} Q^2$$

where $\bar{\nu}$ is the frequency of the transition (in wave numbers) and $Q_{\alpha\beta}^2$ is given by

$$Q_{\alpha\beta}^2 = Q_{(x)\alpha\beta}^2 + Q_{(y)\alpha\beta}^2 + Q_{(z)\alpha\beta}^2$$

where

$$Q_{x(ij)} = e^2 \int \Psi'^*_\alpha \sum_{\bar{}}^{N} x_i \Psi'_\beta \mathrm{d}\tau$$

The contribution to $Q_{x(ij)}$ vanishes except between functions Φ and Φ' which differ in only one orbital, *e.g.*, $A \longrightarrow A'$; the element of Q_x is then given by

$$\sqrt{2}\mathrm{tr}\ \bar{\mathbf{X}}\, \bar{\mathbf{P}}_{AA'}$$

where

$$\bar{\mathbf{P}}_{AA'} = \bar{\mathbf{T}}_A \bar{\mathbf{T}}_{A'}^{\dagger} \text{ and } \bar{X}_{rs} = \int \bar{\phi}_r^* x \bar{\phi}_s \mathrm{d}\tau$$

In the non-orthogonal basis

$$Q_X = \sqrt{2}\mathrm{tr}\ \mathbf{X}\, \mathbf{P}_{AA'}$$

where

$$\mathbf{P}_{AA'} = \mathbf{S}^{-\frac{1}{2}} \bar{\mathbf{P}} \mathbf{S}^{-\frac{1}{2}} \text{ and } X_{rs} = \int \phi_r^* x \phi_s \mathrm{d}\tau = x_{rs} S_{rs}$$

Since x_{rr} is the centroid of orbital r and x_{rs} that of the centroid of bond rs, and since for ordinary $2p$-orbitals these centroids are at the atom and bond mid-points, the calculation in the non-orthogonal basis is straight-forward. It is customary, however,[6] to make similar assumptions when dealing with the orthogonal orbitals which are implicitly accepted as a basis for the SCF calculations and it is therefore useful to compare this " simplified " treatment with that in which there is a rigorous transformation to the ordinary $2p$-basis. The calculated oscillator strengths for the α, p, β, and β' states are given in Table 5.

TABLE 5.

	α	p	β	β'
Calc. from transition charge density	0	0·208	2·175	1·025
Calc. by assuming (orthonormalized) orbitals and overlap distributions centrosymmetric	0	0·205	2·213	1·040

Table 5 shows that the values of the oscillator strengths obtained by the more convenient orthonormal basis without detailed analysis of the transition charge density are in good agreement with those calculated more rigorously (this inference holds good also in the case

[14] Mulliken and Rieke, *Reports Progr. Phys.*, 1941, **8**, 231.

XUM

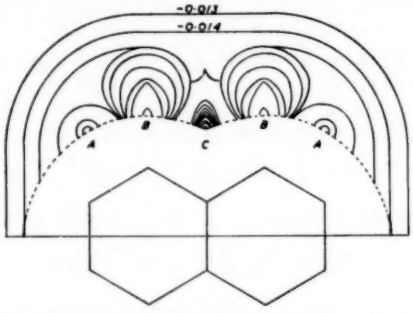
of heteroaromatics [15]). The numerical values given in Table 5 are also in close agreement with those given by Lefebvre and Moser [3] and Pariser.[6]

The Potential Energy outside the Molecule.—The potential energy of a unit-point positive charge moving in the field of the molecule may be represented by

$$V = (\delta_{rs} - q_{rs})/r_{c(rs)} \quad \begin{pmatrix} \delta_{rs} = 1 & r = s \\ \delta_{rs} = 0 & r \neq s \end{pmatrix} \qquad . \quad . \quad . \quad . \quad (2)$$

where $r_{c(rs)}$ is the distance between the point charge and the centroid of bond rs (or the atom if $r = s$) and q_{rs} is the orbital ($r = s$) or overlap ($r \neq s$) charge. Here it is assumed,

Potential energy contours around the naphthalene molecule (in atomic units).



Numerical values (all negative, except as stated) of successive contours, listed outwards are:
A, 0·023, 0·021, 0·016.
B, 0·010 (positive), 0·004, 0·011, 0·013, 0·014, 0·015.
C, 0·026, 0·022, 0·021, 0·020, 0·019, 0·018, 0·017, 0·016.
At ×, *A* 0·028; *C*, 0·028.

provisionally, that each framework ion may be regarded as a point positive charge. This approximation probably holds at distances far enough away for polarisation effects to be small.

The potential field calculated by using expression (2) has an interesting form (see Figure). The broken circles, of radius 5 atomic units, indicate the closest distance at which expression (2) may be meaningful. Of the points which lie on this circle, those opposite to bonds 1—2 and 2—3 have a potential energy twice as large as the point opposite to bond 1—10.

A cation when it enters the potential field of the molecule will become subject to strong directive influences which will tend to attract it towards the bonds. The actual reaction between ligand and molecule will occur at distances so close that expression (2) will not apply and other effects will be significant. No attempt will be made here to discuss the preferential activity of the α-atoms towards cationic substitution. However, it is interesting that the usual assumptions of uniform distribution in unsaturated hydrocarbons, where there are no net charges, lead to no directing influences on an approaching cation.

The author thanks Dr. R. McWeeny for helpful discussions and the Ramsay Memorial Fellowships Trust for the award of a Fellowship.

Department of Chemistry, University College of North Staffordshire,
Keele, Staffordshire. [*Received, April 14th*, 1959.]

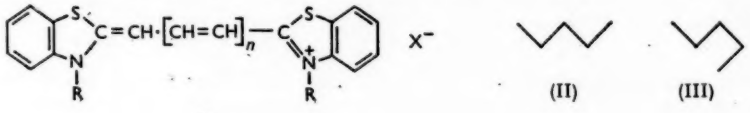
[15] Peacock, unpublished work.

659. *The Crystallography of Some Cyanine Dyes.*

By P. J. Wheatley.

The cell constants and space groups of some cyanine dyes and their solvates have been determined. The structure of the unsolvated dye 3,3′-diethylthiacarbocyanine bromide has been elucidated from two projections. The cation is planar with the conjugated chain in the extended form. The sulphur atoms are *cis* with respect to this chain. Some curious properties of the crystals are described. The results of the structure determination are correlated with other properties of cyanine dyes.

Thiacarbocyanines (I; $n = 1$) are typical of the cyanine dyes used for the sensitization of photographic films.[1] Sensitization consists of two main processes. First, the dye must absorb light in the appropriate region of the spectrum. Secondly, the energy acquired by the dye must be transferred in some way to the photographic emulsion. The first of these processes is well understood. The second is not. On theoretical grounds the cation shown in (I) would be expected to be planar. The planarity of the cation can be destroyed by the introduction of bulky substituents into the central conjugated chain. It has been established that non-planar cyanines are non-sensitizers.[2] Apart from this



(I) (II) (III)

fact, there seem to be few generalizations in the theory of photographic sensitization. For instance, examples are known in which a diethyl-cyanine (R = Et) is an excellent sensitizer, whereas the corresponding dimethyl compound is valueless.[3] Moreover, there appears to be no correlation between the degree of adsorption of the dye on the photographic emulsion and the degree of sensitization conferred.[4] Some dyes that are adsorbed strongly are poor sensitizers; others that are but weakly adsorbed are amongst the best. Finally, most cyanine dyes in solution have the property of forming J-aggregates in which a number of the flat cations are stacked like a pack of cards. But again there is no correlation between the sensitizing power and the capacity to form J-aggregates.

The present investigation was undertaken to establish the molecular configuration of a typical cyanine dye and, possibly, to throw some light on the mechanism of photographic sensitization. The substance finally selected for an *X*-ray structural determination was 3,3′-diethylthiacarbocyanine bromide (I; $n = 1$, R = Et, X = Br). Although there could be little doubt that, except for the methyl groups of the ethyl substituents, the cation would be planar, various conformations were possible. The conjugated chain could be extended (II) or folded (III), and the sulphur atoms could be either on the same side or on opposite sides of either of these chains. Consideration of the non-bonded radii of the atoms suggested that the extended form of the chain was more probable, but the sulphur atoms could still be *cis* or *trans* with respect to this chain.

Experimental

It was difficult to obtain crystals suitable for diffraction purposes. Crystals that had lain for several weeks in a stoppered bottle were apparently perfect with well-defined faces and

[1] Doja, *Chem. Rev.*, 1932, **11**, 273.
[2] Sheppard, Lambert, and Walker, *J. Chem. Phys.*, 1941, **9**, 96.
[3] Brooker, White, Heseltine, Keyes, Dent, and van Lare, *J. Photog. Sci.*, 1953, **5**, 173.
[4] Carroll and West, in "Photographic Sensitivity," ed. Mitchell, Butterworths Scientific Publications, London, 1951, p. 166.

XUM

measurable interfacial angles. However, they showed no extinction in polarized light, and X-ray photographs confirmed almost total structural disorder. Finally, it was found that relatively good photographs could be obtained if the crystals were grown in the dark and transferred rapidly to the diffraction apparatus with a minimum exposure to light. The crystals would remain ordered in the dark indefinitely. As it was not possible to mount the crystals without some exposure to light, however, all X-ray photographs showed some evidence of disorder. The incidence of X-rays appeared to accelerate the disordering process that had already started. Some crystals became disordered so rapidly that little useful crystal information could be obtained. Others could be used to obtain cell dimensions and space groups. A few gave photographs sufficiently good for a structural analysis to be attempted. The useful information

TABLE 1. *Crystallographic constants for some cyanine dyes.*

Compound	n	R	X	Solvent	Formula
(1) 3,3′-Dimethylthiacyanine bromide.....	0	Me	Br	$Ph{\cdot}NH_2$	$C_{17}H_{15}N_2S_2Br,1{\cdot}7C_6H_5{\cdot}NH_2$
(2) 3,3′-Dimethylthiacyanine iodide	0	Me	I	$Ph{\cdot}NH_2$	$C_{17}H_{15}N_2S_2I,1{\cdot}2C_6H_5{\cdot}NH_2$
(3) 3,3′-Diethylthiacarbocyanine bromide	1	Et	Br	Ac_2O	$C_{21}H_{21}N_2S_2Br$
(4) 3,3′-Diethylthiacarbocyanine iodide ...	1	Et	I	MeOH	$C_{21}H_{21}N_2S_2I,CH_3{\cdot}OH$
(5) 3,3′-Diethylthiacarbocyanine bromide	1	Et	Br	EtOH	$C_{21}H_{21}N_2S_2Br,C_2H_5{\cdot}OH$

Space group	a (Å)	b (Å)	c (Å)	α	β	γ	D_m
(1) $P1$ or $P\bar{1}$	10·97	14·64	19·57	107·0°	111·2°	82·7°	1·484
(2) $P2_1/c$	7·26	11·03	31·64	90	99·9	90	1·595
(3) $P2_1/n$	8·24	16·90	14·50	90	94·3	90	1·475
(4) $I2/c$	15·36	18·47	18·26	90	63·3	90	1·545
(5) $P\bar{1}$	8·07	11·83	13·11	98·6	77·2	103·3	1·421

obtained is summarized in Table 1. An additional complicating feature is that the dyes crystallize solvated from a wide variety of solvents. The crystals of 3,3′-dimethylthiacyanine bromide and iodide obtained from aniline appear to contain a non-integral number of solvent molecules. The figures 1·7 and 1·2 in Table 1 are rough values and are the mean of the X-ray and microanalytical results. The fourth entry in Table 1 has been investigated before by optical methods.[5] The earlier work yielded an axial ratio of 0·8317 : 1 : 0·9887 and $\beta = 63°\ 1'$, which may be compared with the ratio 0·8299 : 1 : 0·9867 and $\beta = 63°\ 17'$ obtained by X-rays. The agreement shows that the same substance was being examined in both cases. However, the microanalytical results quoted in the earlier paper indicate unsolvated crystals, whereas the measured values of the volume of the unit cell and of the density ($D_m = 1{\cdot}545$) show that the crystals actually contain methyl alcohol.

The onset of disorder appears to be associated with another curious property of these crystals, that of spontaneous disintegration. Crystals that have been left for some time crumble to a fine powder. The most stable crystals, in this respect, are those of 3,3′-diethylthiacarbocyanine iodide obtained from methyl alcohol. The least stable are those of the bromide of the same dye recrystallized from the same solvent, which fragment as soon as they are removed from the excess of solvent. However, the fragmentation cannot be due solely to loss of solvent from the crystals, since the unsolvated crystals obtained from acetic anhydride show the same property. The disorder manifests itself on Weissenberg photographs as long streaks parallel to the translation direction of the camera. Some of the streaks seem to coincide with Bragg reflexions, but most do not. The crystals used in the present structural investigation, 3,3′-diethylthiacarbocyanine bromide recrystallized unsolvated from acetic anhydride, show a moderate increase of disorder with time. The same crystals used to obtain the X-ray intensities were photographed again six months later. The crystals had partially disintegrated, and the later photographs showed no evidence of Bragg reflexions but only disorder streaks.

Structure Determination.—$C_{21}H_{21}N_2S_2Br$, $M = 445{\cdot}4$. Monoclinic, $a = 8{\cdot}23_7 \pm 0{\cdot}05$, $b = 16{\cdot}90_1 \pm 0{\cdot}08$, $c = 14{\cdot}50_2 \pm 0{\cdot}08$ Å, $\beta = 94°\ 17'$, $U = 2014$ Å^3, $D_m = 1{\cdot}475$ (by flotation), $Z = 4$, $D_c = 1{\cdot}469$, $F(000) = 912$. Space group, $P2_1/n$ (C_{2h}^5, No. 14). Cu-K_α radiation ($\lambda = 1{\cdot}542$ Å), single crystal rotation and Weissenberg photographs.

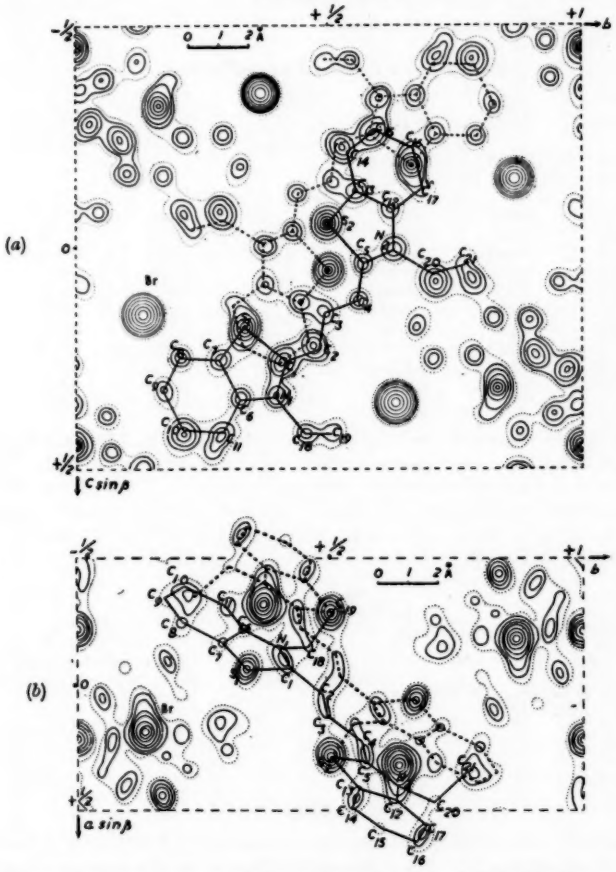
The crystals were needles elongated parallel to the short [a] axis. Multiple-film Weissenberg photographs round [a] were obtained with a square needle about 0·15 mm. across. The $hk0$ photographs were obtained with a cube of side 0·1 mm. cut from a needle. No correction was made for absorption ($\mu = 49{\cdot}3$ cm.$^{-1}$). Relative intensities were estimated by comparison

[5] Mills, *J.*, 1922, **121**, 455.

with standard strips prepared from the same crystals. 227 of the 321 0*kl* reflexions, and 130 of the 183 *hk*0 reflexions obtainable with Cu-K_α radiation were observed to be non-zero.

Each projection was solved in the same manner. A Patterson synthesis gave the co-ordinates of the bromine ion. The phases determined from these co-ordinates were used for a preliminary Fourier synthesis. On the resultant electron-density map the peaks due to the

FIG. 1. (*a*) *Projection of the contents of the unit cell down* [*a*]. (*b*) *Projection of the contents of the unit cell down* [*c*].



(The contours are drawn at equal, arbitrary intervals, except in the bromine peaks, where the intervals are arbitrary and unequal.)

two sulphur atoms could be identified. The phases determined from these three heavy atoms were used to compute a second Fourier synthesis which could readily be interpreted in terms of the whole molecule. Refinement of the 0*kl* projection was carried out by Fourier and difference syntheses. The *hk*0 projection, however, is so poorly resolved that the x co-ordinates of the atoms had to be located from the known y co-ordinates and from standard values of bond lengths and angles. Non-planar models gave significantly worse agreement than planar ones, but little proper refinement could be carried out.

For the 0*kl* projection an isotropic temperature factor $B = 3{\cdot}5$ Å^2 proved adequate to reduce the R factor to 14%. Unobserved reflexions were omitted from the R factors. Refinement

of the *hk*0 projection would not proceed satisfactorily until an anisotropic temperature factor was employed. This was of the form $A + B\cos^2\phi$, where ϕ is the angle between any crystallographic plane and the [*a*] axis.[6] The direction of greatest thermal motion is thus taken to be along [*a*]. The values of *A* and *B* were chosen as 3 and 1·5 Å^2 respectively. The final *R* factor for the *hk*0 projection was 19%. The scattering factors used were those of Berghuis *et al.*[7] for the carbon and nitrogen atoms, that of Tomiie and Stam [8] for the sulphur atom, and that of Thomas and Umeda [9] for the bromide ion. Thomas and Umeda's figures were modified at low values of θ to allow for the additional electron, and corrected for the real part of the dispersion.[10] Since the cation bears a single positive charge, there is a deficiency of one electron spread out over many atoms. This deficiency was ignored.

TABLE 2. *Fractional co-ordinates.*

Atom	*x*/*a*	*y*/*b*	*z*/*c*	Atom	*x*/*a*	*y*/*b*	*z*/*c*
Br	0·190	0·133	0·150$_5$	$N_{(1)}$	0·862	0·396	0·336
				$N_{(2)}$	0·403	0·629	0·006
$S_{(1)}$	0·940	0·333	0·179				
$S_{(2)}$	0·284	0·501	0·947				
$C_{(1)}$	0·937	0·417	0·256	$C_{(11)}$	0·688	0·292	0·418
$C_{(2)}$	0·042	0·481	0·230	$C_{(12)}$	0·458	0·627	0·916
$C_{(3)}$	0·124	0·492	0·146	$C_{(13)}$	0·412	0·553	0·873
$C_{(4)}$	0·225	0·558	0·120	$C_{(14)}$	0·483	0·537	0·787
$C_{(5)}$	0·310	0·570	0·036	$C_{(15)}$	0·576	0·594	0·738
$C_{(6)}$	0·780	0·325	0·342	$C_{(16)}$	0·628	0·667	0·779
$C_{(7)}$	0·817	0·285	0·253	$C_{(17)}$	0·558	0·685	0·867
$C_{(8)}$	0·755	0·205	0·247	$C_{(18)}$	0·852	0·453	0·419
$C_{(9)}$	0·652	0·172	0·321	$C_{(19)}$	0·700	0·506	0·420
$C_{(10)}$	0·627	0·212	0·412	$C_{(20)}$	0·470	0·702	0·057
				$C_{(21)}$	0·344	0·768	0·037

Electron-density maps projected down [*a*] and [*c*] are shown in Fig. 1 (*a*) and (*b*) respectively. The molecule drawn in full lines corresponds to the co-ordinates listed in Table 2. The molecule drawn in dotted lines is centrosymmetrically related to the first. For clarity the molecules related to these two by screw axes and glide planes are not drawn in. A list of observed and calculated structure factors is given in Table 3. The molecular dimensions and the numbering of the atoms are shown in Fig. 2.

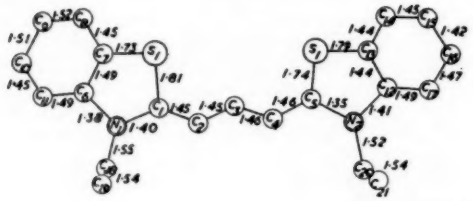


FIG. 2. *The numbering of the atoms and the molecular dimensions.*

DISCUSSION

Within the limits of the experimental results the cation is planar except for the methyl groups of the ethyl substituents. The conjugated chain is in the extended form with the sulphur atoms *cis* with respect to this chain. There appears to be no obvious reason why the *cis*-form should be preferred. In simpler molecules *trans*-configurations are normally found, but it is evident that other factors come into play when steric requirements are no longer dominant. Since the energy barrier resisting conversion from the *cis*- into the *trans*-form must be considerable, it is probable that the cation exists in the *cis*-configuration in solution as well as in the solid.

The internal consistency of chemically similar bonds shows that the C–C and C–N bond

[6] Hughes, *J. Amer. Chem. Soc.*, 1941, **63**, 1737.
[7] Berghuis, Haanappel, Potters, Loopstra, MacGillavry, and Veenendaal, *Acta Cryst.*, 1955, **8**, 478.
[8] Tomiie and Stam, *ibid.*, 1958, **11**, 126.
[9] Thomas and Umeda, *J. Chem. Phys.*, 1957, **26**, 293.
[10] Dauben and Templeton, *Acta Cryst.*, 1955, **8**, 841.

lengths are not accurate to more than 0·1 Å. The accuracy of the lengths of bonds involving sulphur atoms is a little higher. The mean length of the C–S bonds is 1·77 Å, of the C–C bonds in the conjugated chain 1·46 Å, and of the C–C bonds in the benzene rings 1·47 Å. These last two figures are higher than expected, but there is no significant

TABLE 3. *Observed and calculated structure factors for one asymmetric unit*

0kl	F_o	F_c	*0kl*	F_o	F_c	*0kl*	F_o	F_c	*0kl*	F_o	F_c	*hk0*	F_o	F_c	*hk0*	F_o	F_c
0.2.0	5·6	+6·0	1	26·1	−31·3	15	4·5	+5·0	3	7·1	−5·8	5	11·0	−11·3	11	5·4	+5·0
4	11·7	−13·8	2	3·3	+0·3	16	6·3	+5·0	4	9·7	−9·4	6	24·1	−20·4	12	3·8	+0·2
6	28·3	+32·5	3	1·4	−1·1	19	2·4	−3·1	5	4·2	+4·4	7	7·0	+7·2	14	2·7	+2·9
8	11·9	+13·1	4	19·9	+19·0	20	2·2	−2·6	6	1·9	+1·5	8	5·6	+8·4	15	1·6	−1·5
10	6·1	+3·2	5	5·9	+4·5				7	3·5	+2·7	9	4·8	+6·7	16	3·4	+3·0
14	10·6	+10·5	6	10·1	−11·5	0.1.8	10·5	+9·3	8	2·1	+1·9	10	7·2	+10·8			
16	7·9	+7·9	7	12·4	−9·4	3	2·8	+5·3	9	7·8	−8·9	11	11·2	−10·3	5.1.0	13·2	+14·4
18	5·8	+3·0	8	5·1	−6·8	4	8·6	−8·6	11	3·5	−3·0	12	11·3	−11·7	2	4·1	+2·4
20	1·3	−1·4	9	10·4	−8·5	5	12·0	−11·3	12	2·0	−3·0	13	6·8	−7·5	3	5·0	−2·3
			10	9·4	+9·1	6	14·3	−12·3	13	5·6	+5·3	14	12·6	−13·4	4	4·4	−5·5
0.1.1	15·2	−20·5	11	4·6	+1·2	7	4·8	−4·0	16	2·3	−1·6	15	13·5	+12·8	5	1·4	+2·3
2	11·7	−13·0	12	7·1	+8·1	9	8·3	+6·9				16	2·9	+4·5	6	2·3	+3·3
3	10·4	−12·1	13	6·8	+7·8	12	10·9	−9·0	0.1.13	10·5	+10·9	18	2·8	+3·9	7	12·0	+12·7
4	6·2	−5·9	15	2·5	−1·0	13	9·4	−9·3	2	6·1	−5·0	19	3·6	−4·3	8	3·5	+4·2
5	17·8	−18·8	16	6·7	−6·9	18	3·8	−4·7	3	7·3	−6·4	20	1·6	−3·5	9	9·0	+8·7
6	19·8	−20·7							5	2·9	−2·7	21	3·7	+4·3	10	7·3	−6·4
7	1·4	+1·4	0.1.5	7·1	−8·7	0.1.9	5·7	−4·7	6	3·5	+3·8				13	3·1	+2·9
9	4·8	+3·9	2	20·3	−18·3	2	13·5	+12·9	7	3·0	+3·8	2.0.0	27·5	−24·6	14	3·3	+4·5
10	14·7	+14·7	3	2·7	+3·8	3	10·1	+8·6	14	1·2	−0·7	1	13·3	+11·7	15	6·6	+8·9
11	13·3	−13·0	4	7·5	−6·6	4	1·8	−3·6	15	2·1	+3·3	3	2·1	+1·8	16	4·1	−4·0
12	9·0	−10·9	5	6·3	−8·5	5	12·5	+11·8				4	7·1	−3·7			
13	7·1	−4·4	6	18·9	+19·2	6	10·5	−13·4	0.0.14	2·5	+3·1	5	6·2	−5·0	6.0.0	1·7	+3·3
14	13·2	−13·6	7	10·1	−9·5	8	7·3	+7·0	2	3·0	+3·2	6	3·3	−6·2	1	2·1	+1·9
15	3·6	−1·5	9	8·4	+8·0	9	2·3	+0·3	3	1·9	+1·6	7	5·3	−9·2	2	3·4	−1·6
16	8·3	+8·9	10	18·8	−17·8	10	6·9	+4·8	4	2·9	−3·3	8	15·5	−17·2	3	6·2	+6·3
17	4·9	−4·1	11	2·3	−2·0	11	13·2	+12·9	5	4·3	−4·0	9	16·2	+17·9	4	1·6	−1·9
18	1·9	+2·9	12	9·1	+9·4	12	4·9	−6·1	8	7·0	+6·9	10	5·4	−2·8	6	1·9	−0·8
19	3·6	−4·4	14	5·4	+4·6	13	6·4	+6·3	9	6·1	+5·0	11	9·2	+8·4	7	5·7	−4·9
20	3·2	−3·5	15	4·2	+3·8	14	7·3	−6·7	12	5·6	−5·6	12	5·3	+5·2	8	3·7	+5·1
			16	4·7	−5·5	15	1·5	−1·3	13	2·2	−2·4	13	14·7	−17·3	9	4·6	+6·6
0.2.0	17·8	−21·4	18	1·2	−2·7	17	2·3	+1·1				14	14·6	−15·0	10	2·6	−2·1
1	9·7	+14·1	20	4·3	+4·8				0.1.15	2·3	−2·2	16	10·3	−10·2	11	4·0	+4·0
2	11·2	+11·5				0.0.10	23·2	−24·0	2	6·5	+5·9	17	10·8	+11·3	12	3·5	−5·4
3	21·2	+20·3	0.0.6	5·7	+7·4	2	5·0	−2·7	4	3·3	−2·2	18	1·6	−0·8	13	3·7	−5·6
4	22·3	+22·8	1	11·7	−13·3	4	5·8	+4·6	6	6·5	−6·8	20	1·9	−1·9	17	1·8	+3·5
5	28·2	−32·7	2	8·4	−8·8	5	6·5	+3·8	10	1·6	+2·7	21	2·0	−3·0			
6	5·5	−5·5	3	7·7	−5·0	6	6·0	−4·9	12	1·7	−2·6				7.1.0	6·9	−5·8
8	7·9	+8·9	4	35·4	−34·2	7	2·2	+4·2				3.1.0	16·0	−13·6	2	7·4	+7·4
9	24·9	+24·2	5	4·7	+4·7	8	13·2	−11·5	0.0.16	1·3	−1·8	2	2·6	−1·3	3	4·4	−2·0
10	4·2	+4·8	6	14·2	+11·4	9	2·7	−1·3	3	2·2	+3·1	3	8·4	+5·7	4	4·1	−3·7
13	4·0	−5·0	7	11·0	+9·7	10	5·5	−4·5	4	4·4	+4·0	4	1·3	+1·6	5	2·4	−2·8
14	7·7	+6·8	8	8·4	+9·3	11	6·2	+4·9	7	3·8	−2·9	5	4·3	+7·0	9	7·7	−6·9
16	7·7	+6·6	9	3·6	−3·0	14	6·8	−4·6	8	2·6	−4·0	6	2·0	+1·0	11	2·1	+0·9
17	4·7	+7·5	10	14·0	−14·0	15	3·0	−1·0	10	2·0	+2·2	7	25·8	−24·6	15	5·1	−4·4
20	2·4	+2·9	11	3·5	−2·6	16	4·5	−4·6				8	2·6	+0·7			
21	2·5	−3·6	13	6·7	+8·4				0.1.17	5·4	−5·4	9	3·9	−4·0	8.0.0	7·0	−6·8
			14	4·2	−3·7	0.1.11	2·3	+2·3	3	2·6	+3·7	10	3·5	−4·8	2	2·1	+0·6
0.1.3	13·7	−14·7	16	2·3	+3·9	2	3·3	−3·9	7	4·6	−5·3	13	4·8	−6·4	4	2·3	+4·4
2	17·0	+18·6	17	4·6	−5·3	3	18·0	+19·6	*hk0*			14	1·7	+1·4	6	1·8	−2·2
3	13·4	+13·9	20	3·0	−4·3	4	4·8	+4·8	0.3.18	2·2	−3·0	15	9·2	−11·9	9	1·6	−0·7
4	5·6	+5·0				5	9·1	+9·2				16	3·2	−4·3	13	1·5	+0·9
5	25·6	+28·5	0.1.7	12·3	+13·4	6	5·7	+6·1	0.2.0	5·8	+6·1	18	3·8	−3·2			
6	3·7	−2·8	2	8·4	+7·2	7	3·6	−3·7	4	13·3	−14·1	19	1·2	+3·9	9.1.0	2·0	+1·4
7	18·3	−17·8	3	13·0	−15·4	8	4·4	−4·3	6	32·5	+33·7	20	1·2	+2·0	2	1·4	−3·2
9	22·1	−20·7	4	9·2	+7·9	10	5·9	−6·9	8	12·7	+14·0				4	1·6	+1·8
11	12·2	+11·6	5	4·7	−3·3	11	5·7	+6·4	10	6·2	+3·6	4.0.0	2·3	−0·9	5	1·9	+1·8
13	3·9	+2·4	6	3·8	−4·2	12	2·0	+3·0	14	13·0	+12·9	1	20·1	−18·6	6	2·2	+1·2
14	4·0	+3·2	7	17·9	+18·0	13	1·9	+0·7	16	9·7	+10·3	2	9·5	+4·6	7	1·4	+1·0
15	14·5	−15·1	8	1·3	−2·2	14	4·4	+4·1	18	7·2	+4·2	3	7·2	−7·2			
16	2·7	+3·4	9	8·6	+6·6	15	3·2	+2·1	20	2·4	−2·2	4	9·3	+5·9	10.2.10	1·4	+1·0
17	2·1	+2·1	10	6·8	+4·5	16	2·9	−2·5				5	18·3	+18·4	4	1·3	−0·4
19	4·0	+4·7	11	5·1	−6·5				1.1.0	7·6	+10·7	6	5·7	+5·7			
21	3·3	−2·6	12	3·1	−1·8	0.0.12	10·8	+9·2	2	44·8	+48·8	7	3·4	+4·0			
			13	1·5	+0·1	1	4·6	−5·5	3	9·2	−6·6	9	3·1	−4·5			
0.0.4	19·1	−18·0	14	4·1	−4·8	2	7·3	−6·7	4	9·8	+9·7	10	3·8	+2·7			

difference from the standard values. The intermolecular contacts are normal. The four atoms nearest to the bromide ion are $C_{(4)}$, $C_{(11)}$, $C_{(2)}$, and $C_{(19)}$ at 3·58, 3·60, 3·73, and 3·94 Å respectively.

Both methyl groups lie on the same side of the plane of the cation. The planes containing the atoms $N_{(1)}$, $C_{(18)}$, $C_{(19)}$ and $N_{(2)}$, $C_{(20)}$, $C_{(21)}$ are approximately perpendicular to the cationic plane. The cations are stacked in columns up the [*a*] axis, and are best considered in pairs. The pair shown in Figs. 1 (*a*) and (*b*) forms a sort of box with the methyl groups as flaps enclosing the space between the cationic planes. The next pair of cations is obtained by a unit translation along [*a*]. The space between each pair is not enclosed by methyl groups. However, the perpendicular distance between each successive

cationic plane is constant at 3·3 Å, so that the methyl groups cannot be playing any substantial part in determining the distance apart of the cations. The bromide ions lie between the columns.

When dye cations are adsorbed on a photographic emulsion it is generally assumed that they are held with their long axes parallel to the surface and with the nitrogen atoms pointing towards rather than away from the surface.[11] These conclusions were reached from a consideration of the adsorption isotherms, and from the areas of the cation viewed flat, edge on, and end on. The results of the structure analysis show that other arrangements of the adsorbed dye need to be considered. At high concentrations in solution it is probable that columns of cations similar to the columns found in the crystal are formed. Thus a J-aggregate may well consist of dye cations arranged alternately head-to-tail. Similarly, when the dye is adsorbed it seems more probable that this head-to-tail arrangement should be favoured. Further, since the crystal structure shows that the cations have a tendency to associate in pairs across a centre of symmetry, it is possible that the surface, instead of being covered with a " unimolecular " layer of cations edge on, is covered with a double layer of head-to-tail cations with the cationic planes parallel to the surface. Each of these explanations appears to be equally compatible with the evidence so far available, and further experiments will be required to decide between them.

I thank Drs. L. G. S. Brooker and D. W. Heseltine, of Eastman Kodak Company, for many of the crystals and all of the dyes used in this work.

MONSANTO RESEARCH SA.,
BINZSTRASSE 39, ZÜRICH 3/45,
SWITZERLAND.

[*Received, April 15th,* 1959.]

[11] Ref. 4, p. 165.

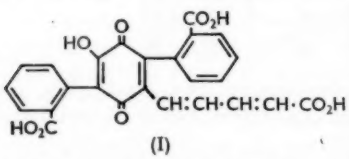
---

660. *Muscarufin. Part I. The Action of Diazotised Anthranilic Acid on* 1,4-*Benzoquinones.*

By R. L. EDWARDS and D. G. LEWIS.

The action of diazotised anthranilic acid on 1,4-benzoquinone and its chloro-, 2,5-dichloro- and 2,6-dichloro-derivatives affords mono- and di-arylated quinones, chlorine usually being replaced.

MUSCARUFIN, the pigment of the cap of *Amanita muscaria* (Linn.) Fries, was assigned structure (I) by Kögl and Erxleben.[1] No synthesis has been reported, although several less complex 2,5-diphenyl-1,4-benzoquinones occurring in fungi have been prepared relatively simply.[2] A synthesis of muscarufin (I) has now been undertaken, involving introduction of *o*-carboxyphenyl groups into appropriate 2-(4-carboxybuta-1,3-dienyl)-1,4-benzoquinones.



(I)

1,4-Benzoquinones have been arylated (*a*) by the Friedel–Crafts reaction,[3] (*b*) by decomposition of diazonium salts in alkaline solution,[4] and (*c*) by use of *N*-nitrosoacylamines.[5] Preliminary experiments indicated that method (*b*) was the most appropriate to the present case. The only instances of its use with diazotised anthranilic acid

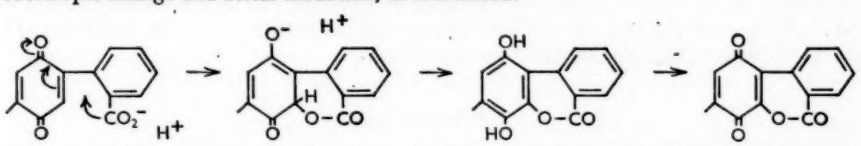
[1] Kögl and Erxleben, *Annalen*, 1930, **479**, 11.
[2] See Thomson, " Naturally Occurring Quinones," Butterworths, London, 1957.
[3] Pummerer *et al.*, *Ber.*, 1922, **55**, 3105; 1927, **60**, 1439; 1933, **66**, 792; Browning and Adams, *J. Amer. Chem. Soc.*, 1930, **52**, 4098; Schildneck and Adams, *ibid.*, 1931, **53**, 2373.
[4] Akagi, *J. Pharm. Soc. Japan*, 1942, **62**, 129, 191, 199.

are those reported by Gunther,[5] who did not investigate the products, and by Bohlmann [6] who obtained an amorphous substance from a reaction with 1,4-benzoquinone, converted by further reactions into crystalline products. We have studied the action of this reagent on 2,5-dichloro-1,4-benzoquinone. By analogy with the syntheses of polyporic acid and atromentin from this quinone we expected *o*-carboxyphenylation at the unsubstituted 3- and 6-position: however, reaction proceeded by replacement of chlorine. This prompted repetition of the reaction with 1,4-benzoquinone, chloro-1,4-benzoquinone, and 2,6-dichloro-1,4-benzoquinone. The reactions with benzoquinone were carried out by two methods; the first is essentially that of Kvalnes, involving use of sodium acetate buffer, and the second, originated by Schimmelschmidt,[7] uses an excess of sodium hydrogen carbonate. The second method demands a water-soluble quinone and therefore could not be applied to the chloroquinones.

2,5-Dichloro-1,4-benzoquinone (XI) with 1 or 2 mols. of diazotised anthranilic acid yielded the orange 2-*o*-carboxyphenyl-5-chloro-1,4-benzoquinone (VIII) and a yellow, chlorine-free compound, insoluble in common organic solvents. The latter gave a purple solution in alkali whence acidification precipitated 2,5-di-*o*-carboxyphenyl-3,6-dihydroxy-1,4-benzoquinone (XIV), and it was therefore the dilactone (VI). These products indicate a stepwise replacement of chlorine, with subsequent ring closure of the disubstituted compound.

Reaction of chloro-1,4-benzoquinone (VII) with 2 mols. of diazotised anthranilic acid led to the same products. Reaction with 2,6-dichloro-1,4-benzoquinone (XV) gave 2-*o*-carboxyphenyl-6-chloro-1,4-benzoquinone (XII) and 2,6-di-*o*-carboxyphenyl-1,4-benzoquinone (XVI). The compounds (VIII), (IX), and (XVI) were recovered unchanged on acidification of their solutions in dilute alkali; they do not possess the lactone structure of (VI). Direct replacement of chlorine is indicated; the only " normal " arylation occurs where positions 5 and 6 are unsubstituted.

The dilactone (VI) is also produced by reaction of diazotised anthranilic acid with 1,4-benzoquinone (see below). It seems probable that 2,5-di-*o*-carboxyphenyl-1,4-benzoquinone is its precursor, and it is significant that the latter has not been found among the products of any reaction in which it might be formed. It is suggested that the dilactone (VI) is produced from 2,5-di-*o*-carboxyphenyl-1,4-benzoquinone by a double process of nucleophilic addition to the β-C atom of the αβ-unsaturated ketone system, followed by prototropic change and aerial oxidation, as illustrated.



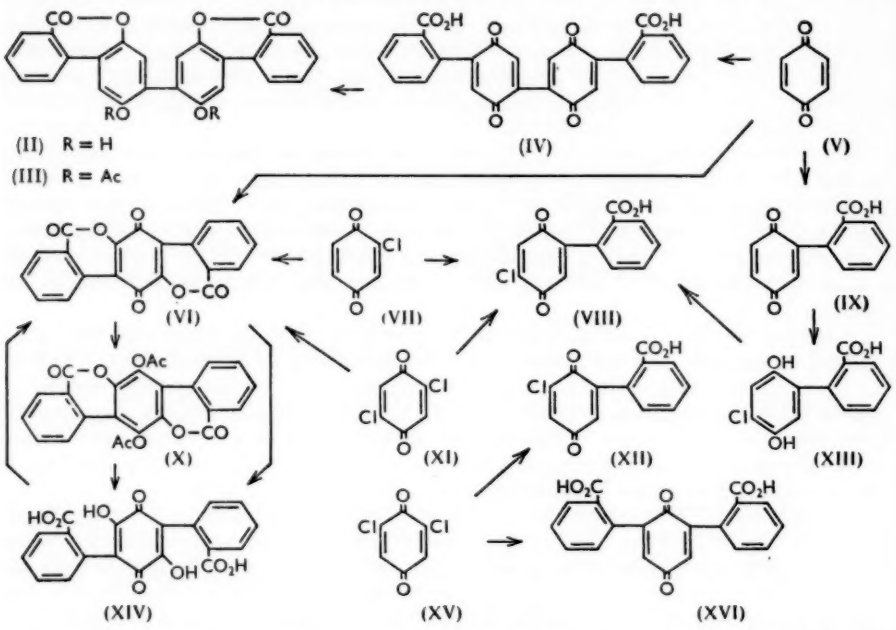
The dilactone (VI), on reductive acetylation, formed the diacetate (X) which yielded 2,5-di-*o*-carboxyphenyl-3,6-dihydroxy-1,4-benzoquinone (XIV) on treatment with alkali. The latter reaction involves hydrolysis to 2′,3′,5′,6′-tetrahydroxy-*p*-terphenyl-2,2″-dicarboxylic acid which is not isolated owing to its rapid aerial oxidation. The quinone (XIV) forms the dilactone (VI) when heated above 300°, as reported by Nilsson,[8] who prepared the quinone by an Ullmann reaction.

Diazotised anthranilic acid (2 mols.) with benzoquinone in the presence of excess of sodium acetate yielded a mixture from which 2′,5′-diacetoxybiphenyl-2-carboxylic acid was obtained by reductive acetylation. Hydrolysis and oxidation of this compound yielded

[5] Gunther, G.P. 679,976; Kvalnes, *J. Amer. Chem. Soc.*, 1934, **56**, 2478; Asano and Kameda, *J. Pharm. Soc. Japan*, 1939, **59**, 768; Ghigi, *Boll. sci. Fac. Chim. ind. Bologna*, 1944—1947, **5**, 38; Wieland and Heymann, *Annalen*, 1935, **514**, 145.
[6] Bohlmann, *Chem. Ber.*, 1957, **90**, 1519.
[7] Schimmelschmidt, *Annalen*, 1950, **566**, 184.
[8] Nilsson, *Acta Chem. Scand.*, 1956, **10**, 1377.

XUM

2-*o*-carboxyphenyl-1,4-benzoquinone (IX). A reaction in which equimolecular proportions were used gave 2-*o*-carboxyphenyl-1,4-benzoquinone directly in better yield. The latter was converted into 2-*o*-carboxyphenyl-5-chloro-1,4-benzoquinone by treatment with hydrogen chloride, followed by oxidation. When arylation of unsubstituted 1,4-benzoquinone was carried out by the Schimmelschmidt procedure a red amorphous solid was obtained. This was converted by reduction and subsequent boiling with alkali into a



yellow crystalline compound of empirical formula $C_{13}H_7O_4$, reduction and reductive acetylation of which gave colourless crystalline compounds of empirical formulæ $C_{13}H_7O_3$ and $C_{15}H_9O_4$ respectively. The yellow compound is a quinone-acid, and structures (IV), (II), and (III) are suggested for these three products.

Experimental

2,5-Di-o-carboxyphenyl-3,6-dihydroxy-1,4-benzoquinone Dilactone (VI).—A solution of 1,4-benzoquinone was prepared by warming to 60° a mixture of quinol (11 g.), potassium bromate (6·1 g.), 2N-sulphuric acid (3 ml.), and water (100 ml.). Cooling gave a fine suspension. A paste prepared by grinding anthranilic acid (26·4 g.) with concentrated hydrochloric acid (50 ml.) and water (80 ml.) was cooled to 0° and treated with an ice-cold solution of sodium nitrite (14·5 g.) in water (175 ml.) with stirring. Saturated sodium acetate solution was added until the solution became alkaline to Congo Red; the mixture was then added all at once to the stirred benzoquinone suspension at 5°. Nitrogen was evolved and a precipitate was formed. Foaming was controlled by pentyl alcohol. The mixture was stirred for 45 min., set aside for 1 hr., and filtered. The precipitate was dried and extracted with boiling acetic acid, the major portion dissolving. The residue was recrystallised from anisole, yielding yellow plates of 2,5-di-*o*-carboxyphenyl-3,6-dihydroxy-1,4-benzoquinone dilactone (0·65 g.), m. p. >400° (Found: C, 69·6; H, 2·1. Calc. for $C_{20}H_8O_6$: C, 69·8; H, 2·3%).

2′,5′-Dihydroxybiphenyl-2-carboxylic Acid.—The crude precipitate (15 g.) from the reaction described above was heated with acetic anhydride (75 ml.) and anhydrous sodium acetate (4 g.) under reflux for 1 hr., during which zinc dust (3 g.) was added in small portions. The

mixture was filtered and the residue was washed with acetic acid. The washings were combined with the filtrate and poured into water (300 ml.), an oil separating which solidified and was recrystallised four times from acetic acid and twice from ethanol to give *2',5'-diacetoxybiphenyl-2-carboxylic acid* as colourless needles (4·5 g.), m. p. 193° (Found: C, 65·1; H, 4·4. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·4%).

The diacetate was heated with 2N-sulphuric acid (75 ml.) and ethanol (60 ml.) for 2 hr. Crystals which separated on cooling recrystallised from ethanol to give the *dihydroxy-acid* as needles (1·65 g.), m. p. 265° (Found: C, 67·9; H, 4·5. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·3%).

o-*Carboxyphenyl*-1,4-*benzoquinone* (IX).—(i) The preceding acid was added in small portions with stirring to nitric acid (5 ml.; *d* 1·42), then poured into water (50 ml.), forming a precipitate of o-*carboxyphenyl*-1,4-*benzoquinone*, which recrystallised from ethanol as orange needles (0·8 g.), m. p. 243°, with darkening and softening at 235° (Found: C, 68·4; H, 3·2. $C_{13}H_8O_4$ requires C, 68·4; H, 3·5%).

(ii) Experiment (i) was repeated with half the quantity of anthranilic acid. The precipitate was separated and dried. A small portion was extracted with light petroleum ether (b. p. 100—120°), the extract yielding crystals on cooling. The bulk of the precipitate was dissolved in acetic acid (100 ml.). Seeding afforded a solid which recrystallised from ethanol, giving orange needles of the quinone (8·4 g.) m. p. 243°.

2,5-*Di*-o-*carboxyphenyl*-3,6-*dihydroxy*-1,4-*benzoquinone* (XIV).—The dilactone (VI) (0·5 g.) was heated in methanol (35 ml.) and 2N-aqueous sodium hydroxide (35 ml.) for 15 min., after which the methanol was allowed to evaporate. The purple solution was acidified with hydrochloric acid; the colour was discharged and 2,5-di-*o*-carboxyphenyl-3,6-dihydroxy-1,4-benzoquinone was precipitated. This was recrystallised three times from dioxan, forming yellow needles, which became orange in air owing to loss of dioxan of crystallisation (0·33 g.), m. p. >400° (Found: C, 63·0; H, 2·6. Calc. for $C_{20}H_{12}O_8$: C, 63·2; H, 3·2%). Attempted recrystallisation from acetic acid gave the quinone dilactone (VI).

2',5'-*Diacetoxy*-3',6'-*dihydroxy*-p-*terphenyl*-2,2''-*dicarboxylic Dilactone* (X).—The dilactone (VI) (0·5 g.) was heated under reflux for 30 min. with acetic anhydride (5 ml.), zinc dust (0·2 g.), and anhydrous sodium acetate (0·1 g.). The mixture was filtered hot; it deposited the *dilactone* (X) on cooling. This recrystallised from *o*-dichlorobenzene as colourless needles (0·46 g.), m. p. 363° (decomp.) (Found: C, 67·0; H, 3·0. $C_{24}H_{14}O_8$ requires C, 67·0; H, 3·3%), dissolving in warm alcoholic alkali to a purple solution, whence acidification precipitated the acid (XIV).

2-o-*Carboxyphenyl*-5-*chloro*-1,4-*benzoquinone* (VIII).—(i) A slow stream of hydrogen chloride was bubbled into a solution of *o*-carboxyphenyl-1,4-benzoquinone (0·5 g.) in chloroform (100 ml.) for 10 min. The precipitated 2-o-*carboxyphenyl*-5-*chloroquinol* recrystallised from ethanol as colourless needles (0·45 g.), m. p. 251° (Found: C, 59·2; H, 3·18; Cl, 13·6. $C_{13}H_9O_4Cl$ requires C, 59·0; H, 3·4; Cl, 13·4%). The quinol (0·2 g.), when warmed with 2N-sulphuric acid (0·2 ml.), water (10 ml.), and potassium bromate (0·15 g.), became red and rapidly yielded 2-o-*carboxyphenyl*-5-*chloro*-1,4-*benzoquinone*, which recrystallised from acetone as orange needles (0·15 g.), m. p. 263°, with sublimation (Found: C, 59·4; H, 2·4; Cl, 13·4. $C_{13}H_7O_4Cl$ requires C, 59·4; H, 2·7; Cl, 13·5%).

(ii) A vigorously stirred solution of chloro-1,4-benzoquinone (VII) (14·2 g.) in ethanol (100 ml.) was treated at 5° with a solution of diazotised anthranilic acid (from 27·1 g. of acid) containing excess of sodium acetate. After 1 hr. the precipitate was separated, washed with ethanol (200 ml.), and heated under reflux with acetone (100 ml.). The insoluble portion was recrystallised three times from anisole to yield the dilactone (VI) as yellow plates, m. p. >400° (Found: C, 69·7; H, 2·3%). Concentration of the acetone solution gave crystals of 2-*o*-carboxyphenyl-5-chloro-1,4-benzoquinone, which recrystallised from acetone as orange needles (3·1 g.), m. p. 263°, undepressed by admixture with the product from (i).

(iii) A solution of 2,5-dichloro-1,4-benzoquinone (XI) (18·5 g.) in ethanol (1600 ml.) was treated at 5° with a solution of diazotised anthranilic acid (from 27·5 g. of acid) containing excess of sodium acetate. Procedure (ii) led to 5-*o*-carboxyphenyl-2-chloro-1,4-benzoquinone (1·75 g.), m. p. and mixed m. p. 263°, and the dilactone (VI) (0·75 g.) (Found: C, 69·6; H, 2·2%).

2-o-*Carboxyphenyl*-6-*chloro*-1,4-*benzoquinone* (XII) *and* 2,6-*Di*-o-*carboxyphenyl*-1,4-*benzoquinone* (XVI).—A stirred solution of 2,6-dichloro-1,4-benzoquinone (XV) (12·2 g.) in ethanol (800 ml.) was treated at 5° with a solution of diazotised anthranilic acid (from 18·2 g. of acid) containing excess of sodium acetate. The mixture was stirred for 3 hr., after which the brown

precipitate was collected, washed with water, dried, and extracted with ethanol (Soxhlet). On cooling, yellow crystals were deposited which, recrystallised from ethanol, gave orange needles of 2-o-*carboxyphenyl*-6-*chloro*-1,4-*benzoquinone* (3·4 g.), m. p. 226° (Found: C, 59·6; H, 2·7; Cl, 13·5. $C_{13}H_7O_4Cl$ requires C, 59·4; H, 2·7; Cl, 13·5%). The residue from the ethanol-extraction crystallised from dioxan, yielding orange-red leaflets of 2,6-*di*-o-*carboxyphenyl*-1,4-*benzoquinone* (1·2 g.), m. p. 399° with softening at 379° (Found: C, 68·6; H, 3·2. $C_{20}H_{12}O_6$ requires C, 69·0; H, 3·5%).

2,2‴-*Dicarboxyquaterphenyl*-2′,5′:2″,5″-*diquinone*.—A solution of *o*-carboxybenzenediazonium chloride prepared from anthranilic acid (70 g.), water (100 ml.), concentrated hydrochloric acid (100 ml.), ice (400 g.), and 40% sodium nitrite solution (70 ml.) was added dropwise with stirring at 5° during 3 hr. to a suspension of 1,4-benzoquinone (21·5 g.) in water (200 ml.) containing sodium hydrogen carbonate (100 g.). The solution was filtered; then acidification with hydrochloric acid gave an amorphous brown precipitate. This material, which could not be crystallised, was warmed with sodium dithionite (25 g.) in 1 : 3 aqueous ethanol (1 l.). The solution was filtered and concentrated to 400 ml.; on cooling, colourless crystals (9·3 g.) separated. Further concentration precipitated a resin. The colourless substance (8 g.) was heated under reflux with 2N-sodium hydroxide (100 ml.) for 1 hr. while air was bubbled through the solution; on cooling and acidification of the solution the *diquinone* crystallised. After three recrystallisations from acetic acid and two from ethanol, it was obtained as yellow plates (5·75 g.), m. p. 389° (Found: C, 68·3; H, 3·3. $C_{26}H_{14}O_8$ requires C, 68·7; H, 3·1%), $\nu_{max.}$ (potassium bromide disc) 1694 (C:O of CO_2H) and 1650 cm.$^{-1}$ (C:O of quinone).

Dilactone (II).—The diquinone (0·5 g.) was heated under reflux for 30 min. with acetic acid (20 ml.) and zinc dust (0·3 g.). The suspension of colourless solid thus formed was decanted from residual zinc and filtered. The solid was washed with water and recrystallised from ethanol and from acetic acid to give the *dilactone* as colourless plates (0·32 g.), m. p. 389° (Found: C, 73·9; H, 3·6. $C_{26}H_{14}O_6$ requires C, 73·9; H, 3·3%). Solutions in alcohol and in acetic acid exhibit a strong violet fluorescence. The *diacetate* (III), prepared by heating the diquinone (0·5 g.) with acetic anhydride and zinc dust, was obtained as colourless needles (0·37 g.) (from acetic acid), m. p. 387° (Found: C, 71·1; H, 3·6. $C_{30}H_{18}O_8$ requires C, 71·1; H, 3·6%).

One of us (R. L. E.) is indebted to Bradford Education Committee and the trustees of the Fred Ellison Scholarship for financial support.

Department of Chemical Technology,
Institute of Technology, Bradford, 7.

[*Received, April 17th,* 1959.]

---

661. *Muscarufin. Part II.** 2-(4-*Carboxybuta*-1,3-*dienyl*)-1,4-*benzoquinones*.

By R. L. Edwards and D. G. Lewis.

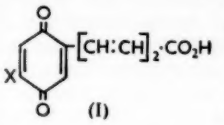
Syntheses of several 5-phenylpenta-2,4-dienoic acids are described. From these 2-(4-carboxybuta-1,3-dienyl)-1,4-benzoquinone and its 5-chloro-derivative have been prepared.

2-(4-Carboxybuta-1,3-dienyl)-1,4-benzoquinone (I; X = H) and its 5-chloro-derivative (I; X = Cl) were required as intermediates in a synthesis of muscarufin. No method for the direct introduction of a pentadienoic acid side-chain into 1,4-benzoquinone has been described. Appropriately substituted 5-phenylpenta-2,4-dienoic acids, which can be converted into the desired quinones, have therefore been prepared. Many methods could be used to make such compounds. Bohlmann [1] has shown the limitations of the Reformatsky reaction between benzaldehydes and γ-bromocrotonic esters; this method was therefore rejected in favour of a two-stage preparation *via* the cinnamaldehyde. The most appropriate cinnamaldehydes, *viz.*, the 2- and 3-hydroxy- and 2,5-dihydroxy-aldehyde, cannot be made from the corresponding benzaldehydes by condensation with

* Part I, preceding paper.

[1] Bohlmann, *Chem. Ber.*, 1957, **90**, 1519.

acetaldehyde in appreciable yield unless the hydroxyl groups are masked, *e.g.*, by formation of the methoxymethyl ethers [2] or glycosides.[3] Overall yields are poor even when this expedient is used. Nitrosalicylaldehydes condense with acetaldehyde,[4] but the resulting nitrocoumaraldehydes are difficult to purify and the yields are *ca.* 5%. Hydroxybenzaldehydes were not investigated further as starting materials. Reactions of nitro- and chloronitro-benzaldehydes with acetaldehyde gave cinnamaldehydes in the following yields: *m*-nitro- 55%, *p*-nitro- 72%, 4-chloro-3-nitro- 72%, and 4-chloro-2-nitro- 73%. The intermediate aldols were dehydrated by means of acetic anhydride without isolation. 2-Nitrocinnamaldehyde was obtained by nitration of cinnamaldehyde in 55% yield.[5]



(I)

Four methods of converting the cinnamaldehydes into phenylpentadienoic acids were examined: (*a*) condensation with acetone, followed by oxidation; (*b*) the Perkin reaction; (*c*) condensation with malonic acid; and (*d*) condensation with pyruvic acid, followed by oxidation. Only method (*d*) gave acceptable yields.

The 5-(nitrophenyl)penta-2,4-dienoic acids were reduced to amino-compounds by ferrous hydroxide in aqueous ammonia. Diazotisation and replacement of the diazonium group by hydroxyl took place in 50—60% yield, except with the 3-amino-4-chloro-compound which gave only a 2% yield of the phenol, probably as a result of loss through diazo-oxide formation.

Potassium nitrosodisulphonate oxidises many phenols to quinones [6] and was used by Bohlmann [7] in the preparation of 2-(4-carboxybuta-1,3-dienyl)-5-methoxy-1,4-benzoquinone (I; X = OMe), but it failed to oxidise the phenols prepared in the present work. Small yields of benzoquinones were obtained by coupling the phenols with diazotised aniline, reduction to *p*-aminophenols, and oxidation. The Elbs persulphate oxidation converted 5-*m*-hydroxyphenylpenta-2,4-dienoic acid into the dihydroxy-compound in moderate yield; the 5-*o*-hydroxyphenylpenta-2,4-dienoic acids, however, gave poor yields of quinols and much resin. Ferric chloride was used to complete the oxidation to quinones.

On treatment with hydrogen chloride in chloroform, 2-(4-carboxybuta-1,3-dienyl)-1,4-benzoquinone gave 2-(4-carboxybuta-1,3-dienyl)-5-chloroquinol, identical with the product of the Elbs oxidation of 5-(4-chloro-2-hydroxyphenyl)-2,4-pentadienoic acid.

Experimental

4-Chloro-3-nitrocinnamaldehyde.—(i) 4-Chlorocinnamaldehyde (4 g.) was added to concentrated sulphuric acid (50 ml.) containing sodium nitrate (1·5 g.) at 0°. The mixture was allowed to attain room temperature (18°) and set aside for 3 hr., then poured on crushed ice (500 g.). The precipitate recrystallised from alcohol, to give almost colourless needles of *4-chloro-3-nitrocinnamaldehyde* (2·8 g.), m. p. 140° (Found: C, 51·4; H, 2·95; N, 6·4; Cl, 16·5. $C_9H_6O_3NCl$ requires C, 51·2; H, 2·8; N, 6·6; Cl, 16·5%).

(ii) 4-Chloro-3-nitrobenzaldehyde (41 g.) was dissolved in acetaldehyde (95 ml.) cooled to 4°. 2% Sodium hydroxide solution (15 ml.) was added dropwise to the stirred solution at 7—10° during 30 min. Acetic anhydride (60 ml.) was added, the excess of acetaldehyde was distilled off, and the solution was boiled under reflux for 45 min. The mixture was poured into 2N-hydrochloric acid (400 ml.), then heated at 100° for 1 hr., cooled, and kept overnight. The precipitate was filtered off and recrystallised from ethanol to give 4-chloro-3-nitrocinnamaldehyde (31 g.), m. p. and mixed m. p. 140°.

4-Chloro-2-nitrocinnamaldehyde (76%) was similarly obtained, as pale yellow needles (from 50% acetic acid), m. p. 117°, from 4-chloro-2-nitrobenzaldehyde (Found: C, 51·1; H, 3·0; N, 6·5; Cl, 16·4%).

[2] Hoering and Baum, G.P. 209,608; Pauly and Wascher, *Ber.*, 1923, **56**, 603.
[3] Tiemann, *Ber.*, 1885, **18**, 3482.
[4] Miller and Kinkelin, *Ber.*, 1887, **20**, 1933.
[5] Davey and Gwilt, *J.*, 1955, 1385.
[6] Teuber *et al.*, *Chem. Ber.*, 1953, **86**, 1036; 1955, **88**, 802.
[7] Bohlmann and Kritzler, *Chem. Ber.*, 1957, **90**, 1512.

5-(*Nitrophenyl*)*penta*-2,4-*dienoic Acids*.—(i) 2-Nitrocinnamaldehyde (24·5 g.) was dissolved in ethanol (200 ml.) and water (100 ml.). The mixture was cooled to 5°, and aqueous sodium hydroxide (9 g. in 100 ml.) was added, followed by pyruvic acid (15 g.) during 30 min. at $<18°$. The mixture was stirred for a further 6 hr. at 18°, then filtered, and the residue of sodium 2-nitrocinnamylidenepyruvate was washed with ethanol (until the washings were colourless) and dried (yield, 20·7 g.). 6-o-*Nitrophenyl*-2-*oxohexa*-3,5-*dienoic acid* was obtained by acidification of an aqueous solution of the sodium salt; it formed yellow plates, m. p. 186°, from ethanol (Found: C, 58·4; H, 3·6; N, 5·4. $C_{12}H_9O_5N$ requires C, 58·3; H, 3·6; N, 5·7%). The sodium salt (19 g.) in water (1 l.) was treated with 30% hydrogen peroxide (13 ml.). After it had been stirred for 3 hr., the mixture was acidified with hydrochloric acid, and the colourless precipitate of 5-*o*-nitrophenylpenta-2,4-dienoic acid (14·1 g.), m. p. 218°, was filtered off, washed with water, and dried.

By the same procedure were prepared: 6-m-*nitrophenyl*-, yellow plates (from ethanol), m. p. 171° (Found: C, 58·5; H, 3·6; N, 5·6%), 6-(4-*chloro*-3-*nitrophenyl*)-, yellow needles (from 50% ethanol), m. p. 191° (Found: C, 51·0; H, 2·8; N, 4·95; Cl, 12·5%), 6-(4-*chloro*-2-*nitrophenyl*)-2-*oxohexa*-3,5-*dienoic acid*, yellow needles (from 50% ethanol), m. p. 176° (decomp.) (Found: C, 51·2; H, 2·6; N, 4·8; Cl, 12·3. $C_{12}H_8O_5NCl$ requires C, 51·2; H, 2·8; N, 5·0; Cl, 12·6%); 5-*m*-nitrophenyl-, pale yellow needles (from acetic acid), m. p. 242° (48% yield from *m*-nitrocinnamaldehyde), 5-(4-*chloro*-2-*nitrophenyl*)-, needles (from alcohol), m. p. 238° (44%) (Found: C, 52·1; H, 3·0; N, 5·2; Cl, 14·1. $C_{11}H_8O_4NCl$ requires C, 52·1; H, 3·2; N, 5·5; Cl, 14·0%), and 5-(4-*chloro*-3-*nitrophenyl*)-*penta*-2,4-*dienoic acid*, yellow needles (from aqueous acetic acid), m. p. 232° (54%) (Found: C, 53·2; H, 3·2; N, 5·4; Cl, 14·0%).

(ii) 2-Nitrocinnamaldehyde (6 g.) was added during 6 hr. to refluxing acetic anhydride (60 ml.) and anhydrous sodium acetate (6 g.). The mixture was heated for a further 18 hr., then poured into water (500 ml.) and set aside. The solid was filtered off and boiled with a 10% solution (100 ml.) of sodium carbonate. The solution was filtered and acidified with dilute sulphuric acid; the precipitate was filtered off and recrystallised from ethanol, giving 5-*o*-nitrophenylpenta-2,4-dienoic acid (2·2 g.), m. p. 218°.

By the same procedure 5-*m*-nitrophenyl-, m. p. 242°, 5-(4-chloro-2-nitrophenyl)-, m. p. 238°, and 5-(4-chloro-3-nitrophenyl)-penta-2,4-dienoic acid, m. p. 232°, were obtained in yields of 24, 25, and 18% respectively.

(iii) 2-Nitrocinnamaldehyde (10 g.), malonic acid (5 g.), and pyridine (6 g.) were heated at 100° for 6 hr., then poured into 2N-hydrochloric acid (100 ml.). The deposited solid was washed with water and dissolved in 10% sodium carbonate solution (150 ml.); the solution was filtered and acidified with dilute sulphuric acid. The precipitated *o*-nitrophenylpenta-2,4-dienoic acid recrystallised from ethanol as almost colourless needles (4·9 g., 40%), m. p. 218°. Yields of other 5-substituted penta-2,4-dienoic acids obtained by this method were: *m*-nitro-, 36%; 4-chloro-2-nitro-, 16%; and 4-chloro-3-nitro-, 17%.

6-*Arylhexa*-3,5-*dien*-2-*ones and* 1,9-*Diarylnona*-1,3,6,8-*tetraen*-5-*ones*.—2-Nitrocinnamaldehyde (20 g.) was warmed with ethanol (680 ml.) and water (120 ml.) until a clear solution was formed. This was cooled to 20°, and acetone (20 g.) was added, followed by 10% sodium hydroxide solution, with stirring, until the solution was alkaline to litmus. The mixture was stirred for 2 hr. at 20°, and the precipitate was filtered off, washed with water, dried, and recrystallised from ethanol to give pale yellow needles of 1,9-diphenylnona-1,3,6,8-tetraen-5-one (11·4 g.), m. p. 208°. The filtrate was poured into water (2 l.) and set aside for 14 hr. The precipitated 6-arylhexa-3,5-dien-2-one was filtered off, washed with water, dried, and recrystallised from ethanol, forming pale yellow needles (4·4 g.), m. p. 73°.

Similarly were obtained the 6-m-*nitrophenyl* (3·0 g. from 20 g.), m. p. 100·5°, yellow needles (from ethanol) (Found: C, 66·2; H, 5·0; N, 6·4. $C_{12}H_{11}O_3N$ requires C, 66·4; H, 5·1; N, 6·45%), and 1,9-*di*-m-*nitrophenyl* (14·2 g.), m. p. 199°, yellow needles (from ethanol) (Found: C, 66·8; H, 4·3; N, 7·2. $C_{21}H_{16}O_5N_2$ requires C, 67·0; H, 4·25; N, 7·45%), 6-(4-*chloro*-2-*nitrophenyl*) (2·8 g. from 24 g.) m. p. 112°, pale yellow needles (from ethanol) (Found: C, 57·0; H, 4·3; N, 5·5; Cl, 13·9. $C_{12}H_{10}O_3NCl$ requires C, 57·25; H, 4·0; N, 5·6; Cl, 14·1%), and 1,9-*di*-(4-*chloro*-2-*nitrophenyl*) (1·0 g.), m. p. 246°, yellow needles (from acetic acid) (Found: C, 56·4; H, 3·2; N, 6·3; Cl, 15·7. $C_{21}H_{14}O_5N_2Cl_2$ requires C, 56·6; H, 3·15; N, 6·3; Cl, 15·95%), 6-(4-*chloro*-3-*nitrophenyl*) (0·8 g. from 24 g.), m. p. 124°, pale yellow needles (from ethanol) (Found: C, 57·1; H, 4·2; N, 5·5; Cl, 14·0%), and 1,9-*di*-(4-*chloro*-3-*nitrophenyl*) *compound* (2·4 g.), m. p. 239°, pale yellow needles (from ethanol) (Found: C, 56·5; H, 2·9; N, 6·2; Cl, 15·85%).

5-(*Aminophenyl*)*penta*-2,4-*dienoic Acids*.—To 5-*o*-nitrophenylpenta-2,4-dienoic acid (2·2 g.) in N-ammonia (200 ml.), ferrous sulphate heptahydrate (16·7 g.) in water (50 ml.) was added, the mixture was warmed to 60° for 15 min., with stirring, then filtered, and the precipitate was washed several times with hot water. The filtrate, combined with the washings, was concentrated to 60 ml. The crystals which were deposited were filtered off from time to time, and after the concentrated solution had cooled, recrystallised from ethanol, giving 5-*o*-aminophenylpenta-2,4-dienoic acid as yellow plates (1·7 g.), m. p. 175°. Similarly, 5-*m*-aminophenylpenta-2,4-dienoic acid was obtained as yellow needles (from ethanol), m. p. 178°, in 70% yield.

5-(2-*Amino*-4-*chlorophenyl*)*penta*-2,4-*dienoic acid* formed yellow needles (from ethanol), m. p. 239° (56% yield) (Found: C, 59·05; H, 4·3; N, 6·4; Cl, 15·9. $C_{11}H_{10}O_2NCl$ requires C, 59·1; H, 4·5; N, 6·5; Cl, 15·9%) its *acetyl derivative* crystallised from ethanol as pale yellow needles, m. p. 291° (Found: C, 58·6; H, 4·6; N, 5·2; Cl, 13·0. $C_{13}H_{12}O_3NCl$ requires C, 58·8; H, 4·4; N, 5·3; Cl, 13·4%). 5-(3-*Amino*-4-*chlorophenyl*)*penta*-2,4-*dienoic acid* formed yellow needles (from ethanol), m. p. 237° (55%) (Found: C, 58·9; H, 4·5; N, 6·3; Cl, 15·75%) [*acetyl derivative*, pale yellow needles (from ethanol), m. p. 284° (Found: C, 58·8; H, 4·5; N, 5·5; Cl, 13·25%)].

5-(*Hydroxyphenyl*)*penta*-2,4-*dienoic Acids*.—5-*o*-Aminophenylpenta-2,4-dienoic acid (1·1 g.), sodium carbonate (0·3 g.), and sodium nitrite (0·35 g.) were dissolved in water (50 ml.), and the solution was poured into a stirred mixture of ice (10 g.) and concentrated hydrochloric acid (5 ml.). The mixture was diluted with water (100 ml.) and added at 3—4 drops per min. to a boiling solution of sodium sulphate (250 g.) and concentrated sulphuric acid (5 ml.) in water (200 ml.), which was agitated and kept boiling by introduction of steam. The addition was made through a tube surrounded by a cold-water jacket, which extended almost to the surface of the hydrolysing medium. A few minutes after the addition was complete the solution was cooled and set aside for several hours. The yellow crystalline precipitate was filtered off, washed with water, and recrystallised from acetic acid to give 5-*o*-*hydroxyphenylpenta*-2,4-*dienoic acid* as yellow needles (0·6 g.), m. p. 237° (Found: C, 69·7; H, 5·4. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%). The *acetyl* derivative crystallised from benzene in colourless needles, m. p. 182° (Found: C, 67·2; H, 5·2. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%).

The same procedure gave 5-m-*hydroxyphenyl*- (55%), almost colourless needles (from water), m. p. 209° (Found: C, 69·5; H, 4·9%), 5-(4-*chloro*-2-*hydroxyphenyl*)- (52%), yellow needles (from acetic acid), m. p. 243° (Found: C, 58·9; H, 4·2; Cl, 15·7. $C_{11}H_9O_3Cl$ requires C, 58·8; H, 4·0; Cl, 15·8%), and 5-(4-*chloro*-3-*hydroxyphenyl*)-*penta*-2,4-*dienoic acid* (2%), m. p. 224°, colourless needles from ethanol (Found: C, 59·0; H, 4·2; Cl, 15·8%). The *acetyl derivatives*, prepared in the usual way, formed needles, m. p. 160° (from benzene) (Found: C, 67·1; H, 5·3. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%), m. p. 228° (from ethanol) (Found: C, 58·7; H, 4·5; Cl, 13·6. $C_{13}H_{11}O_4Cl$ requires C, 58·8; H, 4·1; Cl, 13·3%), and m. p. 227° (from benzene) (Found: C, 58·8; H, 4·3; Cl, 13·2%), respectively.

5-(2,5-*Dihydroxyphenyl*)*penta*-2,4-*dienoic Acids*.—5-*o*-Hydroxyphenylpenta-2,4-dienoic acid (5·7 g.), dissolved in 10% sodium hydroxide solution (50 ml.), was cooled to 10°. Potassium persulphate (7 g.) in water (250 ml.) was added during 2 hr., with stirring. After 14 hr. the solution was acidified to Congo Red with hydrochloric acid. The precipitate was filtered off. The solution was then made acid to litmus, and heated at 100° for 1 hr., then cooled, and extracted with ether. The extract was dried, and the ether was removed, leaving a solid which recrystallised from acetic acid to give yellow needles of 5-(2,5-*dihydroxyphenyl*)*penta*-2,4-*dienoic acid* (0·4 g.), m. p. 225° (Found: C, 63·8; H, 4·85. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·85%).

By the same procedure 5-*m*-hydroxyphenylpenta-2,4-dienoic acid (5·8 g.) gave the same product (1·4 g.). 5-(4-Chloro-2-hydroxyphenyl)- (5·8 g.) gave 5-(4-*chloro*-2,5-*dihydroxyphenyl*)-*penta*-2,4-*dienoic acid* (0·2 g.), yellow needles (from acetic acid), m. p. 254° (Found: C, 54·6; H, 3·6; Cl, 14·8. $C_{11}H_9O_4Cl$ requires C, 54·9; H, 3·7; Cl, 14·7%).

2-(4-*Carboxybuta*-1,3-*dienyl*)-1,4-*benzoquinone*.—5-(2,5-Dihydroxyphenyl)penta-2,4-dienoic acid (4·2 g.) was treated in water (200 ml.) at 60° with aqueous ferric chloride (11 g. in 200 ml.). After 5 min. the brown precipitate was filtered off, washed with water, and dissolved in hot ethanol (30 ml.). On cooling, the red 2-(4-*carboxybuta*-1,3-*dienyl*)-1,4-*benzoquinone* crystallised. This recrystallised from ethanol as red needles (2·1 g.), m. p. 166—168° (decomp.) (Found: C, 64·6; H, 4·1. $C_{11}H_8O_4$ requires C, 64·7; H, 3·9%).

2-(4-*Carboxybuta*-1,3-*dienyl*)-5-*chloro*-1,4-*benzoquinone*.—(i) By the above procedure 5-(4-chloro-2,5-dihydroxyphenyl)penta-2,4-dienoic acid (2·4 g.) gave 2-(4-*carboxybuta*-1,3-*dienyl*)-5-*chloro*-1,4-*benzoquinone* as orange needles (1·3 g.) (from ethanol), m. p. 188° (Found: C, 55·1; H, 3·05; Cl, 14·8. $C_{11}H_7O_4Cl$ requires C, 55·3; H, 2·9; Cl, 14·9%).

(ii) Aniline (0·5 g.) in concentrated hydrochloric acid (1·25 ml.) and water (1·25 ml.) was treated at $<5°$ with sodium nitrite (0·35 g.) in water (1 ml.). After 10 min. it was added slowly to an ice-cold stirred 5-(4-chloro-2-hydroxyphenyl)penta-2,4-dienoic acid (1·15 g.) in 10% sodium hydroxide solution (3·6 ml.) containing sodium carbonate (0·05 g.). The mixture was stirred for 3 hr. at 0—5°; 50% sodium hydroxide solution (2 ml.) was then added, the solution was warmed to 80°, and sodium dithionite solution was added dropwise until the colour was discharged. Aniline was removed in steam, and the residue made acid to Congo Red. The yellow precipitate of 5-(5-amino-4-chloro-2-hydroxyphenyl)-2,4-pentadienoic acid was filtered off, washed with water, dissolved in water (250 ml.), and warmed with ferric chloride (11 g.) and concentrated hydrochloric acid (5 ml.) in water (100 ml.). The precipitate formed was separated and recrystallised twice from ethanol, to give the quinone as orange needles (0·06 g.), m. p. 188°.

(iii) 2-(4-Carboxybuta-1,3-dienyl)-1,4-benzoquinone (1·2 g.) was suspended in chloroform (100 ml.), and hydrogen chloride was bubbled through the mixture for 5 min. After 10 hr. the precipitated 5-(4-chloro-2,5-dihydroxyphenyl)penta-2,4-dienoic acid was filtered off, and recrystallised from acetic acid to give yellow needles (1·05 g.), m. p. and mixed m. p. 254°. Oxidation with ferric chloride, as described previously, gave the quinone as orange needles (0·57 g.) (from alcohol), m. p. 188°.

One of us (R. L. E.) is indebted to the Bradford Education Committee and the trustees of the Fred Ellison Scholarship for financial support.

Department of Chemical Technology,
Institute of Technology, Bradford, 7. [*Received, April 17th*, 1959.]

---

662. *Autoxidation. Part I. Liquid-phase Autoxidation of 5-Methylnonane.*

By R. R. Arndt, J. B. Barbour (in part), (Miss) E. J. Engels, D. H. S. Horn, and D. A. Sutton.

Gas chromatography, in conjunction with a highly sensitive flame ionisation detector and infrared spectroscopy, has been used to analyse the mixture of reduced autoxidation products of 5-methylnonane, and so determine the relative susceptibilities of the various carbon atoms to attack. It is calculated that at minimum reaction a hydrogen atom of a tertiary carbon atom is removed nineteen times as fast as a hydrogen of a normal secondary one. The latter hydrogen atom is in turn removed four times as fast as one attached to a primary carbon atom. A large proportion of the product was composed of disubstituted derivatives produced by α-, β-, and γ-intramolecular hydrogen transfer.

Valuable studies have been made recently by Twigg,[1] Benton and Wirth,[2] Pritzkow,[3] and Wibaut and Strang [4] of the position of radical attack on straight-chain hydrocarbons during autoxidation. The purpose of the present work has been to determine the effect, on the susceptibility of the various positions to attack, of the introduction of a methyl group into an otherwise straight-chain hydrocarbon. Hydrocarbons containing a single methyl branch or a limited number of branches, are present in considerable amounts

[1] Twigg, *Chem. Eng. Sci., Special Suppl.*, 1954, **3**, 5.
[2] Benton and Wirth, *Nature*, 1953, **171**, 269.
[3] Pritzkow and Müller, *Annalen*, 1955, **597**, 167; Langenbeck and Pritzkow, *Fette u. Seifen*, 1953, **55**, 435.
[4] Wibaut and Strang, *Proc. K. Ned. Akad. Wet.*, 1953, Series B, **56**, 340 and earlier references.

in the hydrocarbon mixture produced by the Fischer–Tropsch synthesis.[5] A study has accordingly been made of the branched-chain hydrocarbon 5-methylnonane.

Pure 5-methylnonane was oxidised at 90° in oxygen. Samples were withdrawn at intervals for analysis and for reduction with lithium aluminium hydride to convert the products, assumed to be hydroperoxides, ketones, esters, and acids, into a mixture of the corresponding 5-methyl-nonanols and -nonanediols; short-chain alcohols derived from chain-fission products, and unchanged hydrocarbon were also present.

Attempts were first made to analyse this mixture, after preliminary fractionation, by infrared or mass spectroscopy, but the mono- and di-substituted products could not be isolated quantitatively. This difficulty was overcome by analysing the mixture directly by means of gas chromatography with the aid of a highly sensitive flame ionisation detector.[6] This method had the advantage that partial analyses could be made at low oxidation levels, where the effect of secondary transformations involving fission were at a minimum, and that the more efficient column packings containing relatively small proportions of liquid phase [7] could be used. A large number of possible reduced products was synthesised for identification of the chromatographic peaks.

On chromatography of the reduced mixture, any fission products were eluted first, followed, in order and with complete resolution, by the unchanged paraffin, 5-methylnonan-5-ol, a mixture of the 3- and the 4-alcohols, then the 2-, 1-, and side-chain alcohol, followed by a group of four diols corresponding to 5-methylnonane-4,5- and -3,5-diol, an unidentified diol or diol mixture (present in significant amounts only at higher levels of autoxidation), and the 2,5-diol.

Trial runs with a 5% solution of an artificial mixture of 5-methylnonanols in 5-methylnonane (see Table 1) indicate the accuracy of the method.

A similar accuracy was achieved by gas chromatography of an artificial mixture of 5-methylnonane-2,5-, 3,5-, and -4,5-diol and 5-methylnonan-1-ol.

The analyses of the reduced autoxidation mixtures are shown in Table 2. Some of these were obtained after preliminary separation of larger amounts of reduced products by distillation and partition chromatography into monol and diol groups for further characterisation. The mixture of 3- and 4-alcohols could not be resolved by gas chromatography, but it was possible, when sufficient material was available, to determine the proportion of the isomers present in the gas-chromatographic fraction by means of infrared absorption spectroscopy. One partial analysis was made at a level where peroxides only could be detected (Table 2, B1).

TABLE 1. *Analyses of an artificial mixture of 5-methylnonanols.*

	5-ol	4- + 3-ol	2-ol	1-ol	Side-chain alcohol
Taken (%)	39	25	23	4	10
Found (%)	41	25	23	3	8
	40	25	23	3	7
	41	25	22	3	9

Whereas the susceptibility of the various carbon positions to attack was in the expected order, tertiary > secondary > primary, unexpected differences in the reactivity of the secondary carbon atoms were found. Position 2 was slightly more attacked than position 4, and both these were attacked 2—3 times as much as position 3. This could have been due to the ready removal, by a 3-peroxy-radical, of hydrogen from the active position 5 by β-intramolecular hydrogen-transfer,[1] so that a difunctional rather than a monofunctional 3-derivative was formed. This is unlikely, however, since 5-methylnonane-3,5-diol was present in relatively small proportions in the diol mixture. Alternatively, the most

[5] Weitkamp, Seelig, Bowman, and Cady, *Ind. Eng. Chem.*, 1953, **45**, 343.
[6] Harley, Nel, and Pretorius, *Nature*, 1958, **181**, 177.
[7] Cheshire and Scott, *J. Inst. Petroleum*, 1958, **44**, 74.

XUM

TABLE 2. *Analyses of reduced autoxidation products.*

Expt.	B				A		C		D	
Wt. oxidised	100 g.				140 g.*		25 g.		25 g.	
Sample	B1	B2	B3	B4	A1	A2	C1	C2	D1	D2
O_2 Absorption (mol. %)	0·3	1·1	2·4		2·3		8·5		13·8	
RO·OH (mol. %)	0·3	0·7	1·4		1·5		2·0		2·3	
Ketone (mol. %)	—	0·1	0·3		0·5		3·2		5·0	
Monols (%)	75	—	73	—	74	—	73	—	71	—
Diols (%)	25	—	27	—	26	—	27	—	29	—
Composition (%) of mono-alcohols										
5-ol	60	56	47	48 †	43	43 †	38	39 †	38	30 †
4-ol	20 ‡	21 ‡	27 ‡	18	27 ‡	20	29 ‡	17	31 ‡	21
3-ol				7		9		12		13
2-ol	13	15	19	19	21	21	23	23	22	26
1-ol	5	5	5	5	6	5	7	6	6	7
Side-chain alcohol	2	3	2	3	3	2	3	3	3	3
Composition (%) of di-alcohols										
2,5-diol	57	—	54	—	53	—	53	—	51	—
3,5-diol	26	—	25	—	25	—	26	—	25	—
4,5-diol	10	—	7	—	6	—	3	—	5	—
Unknown diols (?) (%)	7	—	14	—	16	—	18	—	19	—

* In ultraviolet light. † Monol concentrate. ‡ Too little for determination of 3:4-monol ratio.

stable conformations are expected to be those in which the position 3 is less accessible to attack by bulky alkoxy-radicals than the other secondary positions.

As would be expected, the three primary positions are equally attacked. The relative rates of attack of the unhindered positions at the lowest levels of reaction are calculated to be as follows: hydrogen is removed nineteen times more readily from a primary than a secondary (Twigg [1] has reported a value of about 20) and from a secondary four times as fast as from a primary carbon atom.

The apparent decrease in the amount of 5-alcohol and attack at position 5 with increasing oxygen absorption (see Table 2) is undoubtedly due to the increasing decomposition of the 5-peroxides to ketonic fragments, the amount of ketone increasing rapidly at higher oxidation levels. Reduction products of these substances, eluted before the methylnonanols, were found in increasing amounts as the reaction proceeded. Ethanol, butan-1-ol, and hexan-2-ol were the major substances detected and are clearly derived from chain-fission products of the most abundant product, 5-hydroperoxy-5-methylnonane: $Bu_2CMe{\cdot}O{\cdot}OH \longrightarrow BuCOMe + HOBu$. Removal of the methyl group, to yield nonan-5-one, is not favoured as no nonan-5-ol could be detected. This is in conformity with George and Walsh's rule [8] that cleavage of a tertiary peroxide occurs in such a way that the longer alkyl group bound to the oxygen-carrying carbon is separated.

A relatively large proportion of disubstituted autoxidation products was found, indicating that the chain reaction step, $RO{\cdot}O{\cdot} + HR \longrightarrow RO{\cdot}OH + {\cdot}R$, is propagated to a considerable extent by intramolecular elimination of hydrogen, as suggested by Twigg.[1] The ingenious work of Rust [9] leads to the conclusion that hydrogen is most easily removed from the β-, and next most easily from the γ-carbon atom. However, Twigg concluded that little α- or β-attack takes place when n-decane is autoxidised. On the other hand, 5-methylnonane has been found to undergo more γ- than β-intramolecular attack, 2—3 times more 2,5- than 3,5-diol being formed. These differences are most likely to be due to differences in conformation, produced by increasing chain-branching, the presence of two close methyl branches, as in Rust's hydrocarbons,[9] being most effective in producing β-attack.

The amount of 5-methylnonane-4,5-diol formed was relatively small, indicating that

[8] George and Walsh, *Trans. Faraday Soc.*, 1946, **42**, 94, 264.
[9] Rust, *J. Amer. Chem. Soc.*, 1957, **79**, 4000.

α-intramolecular attack is also possible but not favoured. At higher levels of oxidation, other diol peaks appeared in the gas chromatograms. These were not identified but are doubtless due to the formation of diols by intermolecular double attack.

An attempt was made to determine partially the composition of the diols by converting the diols having a 5-hydroxy-group, first into the 5-chloro-alcohols by concentrated hydrochloric acid, then into the monols by hydrogenation. The 3,5- and 4,5-diols were quantitatively converted in this way into the 3- and 4-monols respectively but the 2,5-diol was probably converted into a pentane-insoluble tetrahydrofuran oxonium salt, which on neutralisation reverted to the original diol.[10]

Experimental

Precise distillations were carried out in column " A " (a Heli-grid column, 13 mm. i.d., 3 ft. in length,[11] supplied by Messrs. Podbielniak Inc., Chicago, U.S.A.), and column " B " (a micro spinning-band column [12]).

Pure 5-methylnonane, prepared as described below, was autoxidised in an electrically heated silica flask fitted with a thermometer and a side-arm holding a fine capillary for withdrawal of samples without interruption of the reaction. The flask was connected to a gas burette, and the contents were stirred magnetically and kept at 90° by means of an electrically heated jacket.

Preparation of the Products for Analysis.—Samples (*ca.* 1 c.c.), withdrawn at different stages, were analysed for peroxides iodometrically [13] and for ketones by comparing the intensity of the infrared absorption in the 5·85 μ region with that of 5-methylnonan-3-one dissolved in 5-methylnonane. Acids and esters were determined by acid and saponification values: at low levels of oxidation negligible amounts were present.

For gas chromatography the samples were diluted with dry ether and reduced with lithium aluminium hydride. The products were recovered by addition of dilute sulphuric acid. The ether extract was dried (Na_2SO_4), and the ether distilled off through a short column. The residue was analysed directly. Where larger samples were available at the end of the reaction, the reduced product was fractionated in column " B " into unchanged hydrocarbon, monoalcohols (b. p. 71—104°/10·5 mm., n_D^{30} 1·4236—1·4317) and dialcohol residue. The alcohol fractions were further purified by chromatography in 80% ethanol on a reversed-phase partition column prepared from non-wetting Supercel [14] (12 g.) and isoheptane (12 g.). The alcohols were located in the eluate (collected in 2 ml. fractions) by refractive-index measurements and spot tests with the Komarowski reagent.[15] The combined alcohol fractions were diluted with an equal volume of water and extracted several times with pentane. Evaporation of the pentane yielded either the monol mixture (0·5—1 g.), n_D^{30} 1·4330 (Found: C, 75·5; H, 13·9; active H, 0·68. Calc. for $C_{10}H_{22}O$: C, 75·9; H, 14·0; active H, 0·63%), or the diol mixture (0·35 g.), n_D^{30} 1·4387. The latter was found by gas chromatography still to contain about 10% of monols (Found: C, 69·7; H, 12·8; active H, 1·17. Calc. for $C_{10}H_{22}O_2$: C, 68·9; H, 12·7; active H, 1·16. Calc. for a 1 : 9 monol–diol mixture: C, 69·6; H, 12·9; active H, 1·11%).

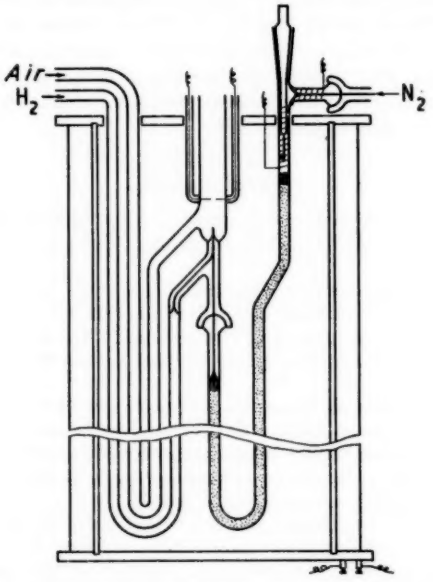
Gas-chromatographic Apparatus.—An apparatus, shown in the Figure, was constructed, incorporating a modified form of the flame ionisation detector of Harley *et al.*[6] For high-boiling substances it was necessary to place the flame and electrodes well inside the heating jacket. The electrodes were made of platinum wire (0·5 mm. diam.), set in the opposite sides of the glass chimney 1·0—1·5 mm. apart and 1·0—1·5 * mm. above the flame jet. To avoid electrical interference from the heating jacket the electrodes were housed in thin glass tubes covered with woven-wire screening to the point of union with the chimney. The flow of hydrogen and of nitrogen were controlled with " Precision Regulator Valves " supplied by Negretti and Zambra Ltd., London. The air-flow was controlled with a pinch-cock. All three gas flows were measured by rotameters supplied by Emil Greiner and Co., New York, U.S.A. The voltage

* *Added in proof:* Owing to an error in drawing, this distance is shown too large in the Figure.

[10] Froebe and Hochstetter, *Monatsh.*, 1902, **23**, 1088.
[11] Podbielniak, *Ind. Eng. Chem., Analyt.*, 1941, **13**, 639.
[12] Horn and Hougen, *J.*, 1953, 3535.
[13] Sully, *Analyst*, 1954, **79**, 86.
[14] Howard and Martin, *Biochem. J.*, 1950, **46**, 532.
[15] Rosenthaler and Vegezzi, *Branntweinwirtschaft*, 1953, **75**, 68; cf. *Chem. Abs.*, 1953, **47**, 7373.

XUM

to the detector circuit was stabilised with a " Stabiline " automatic voltage regulator, supplied by Superior Electric Co., Bristol, Conn., U.S.A. The nitrogen used was freed from oxygen by passing it over copper turnings at 400°.



The substance to be chromatographed was put on the column by stopping the nitrogen flow and replacing the B7 stopper by one fitted with a platinum loop filled with the liquid (0·2 mg.) to be chromatographed. For the detection of the monols, present as a 5% solution in 5-methylnonane, a larger loop of flattened wire holding 1—2 mg. was used. The tube surrounding the loop was heated with a wire coil to about 20—50° above the temperature of the jacket. This system was the most satisfactory for the introduction and rapid vaporisation of small amounts of liquids, essential with a detector of high sensitivity. Immediately the stopper was replaced, the nitrogen flow was restarted. The optimum flow rates of 28, 25, and 700 ml./min., for nitrogen, hydrogen, and air respectively, were used. The flame was simply ignited from the top of the chimney. The zero detector signal (base line) was normally independent of the column temperature or small variations in gas flows. However, it became sensitive to nitrogen flow rate if " bleeding " of the liquid phase took place. The columns, easily interchangeable by releasing the ball joints, were made of U tubes (50 cm. long, 4 mm. int. diam.). Coiled columns gave poorer resolution. The columns were packed under a vacuum with vibration. For the analysis of the monols a packing of polyethylene glycol 400 (manufactured by Olin Mathieson Chem. Corp., U.S.A.), 7% on " Embacel " (a purified kieselguhr, 60—100 mesh, supplied by May and Baker Ltd., England), was used with a column temperature of 80°. For the analysis of the diols a packing of polyethylene glycol 400, 5% on " Embacel," was used with a column temperature of 115°. For the analysis of the short-chain alcohol fragments a 5% 3-m. polyethylene glycol column at 80° was used.

Infrared Analysis of the 3-4-*Monol Mixture.*—A " Vapour Fractometer " Model 154B, supplied by Perkin-Elmer Corp., Norwalk, Conn., U.S.A., was modified so that the outlet from the detector cell was connected directly to a collection trap, by means of a short, electrically heated (to prevent condensation of the monols) pipe ($\frac{1}{8}$" diam.). The monol mixture (40—50 mg.) in heptane (200 mg.) was chromatographed at 130° on a column (4 mm. diam., 3 m. long), packed with 1 : 5-polyethylene glycol 400–" Celite " (100 mesh) and a nitrogen flow rate of 20 ml./min. A high proportion of liquid phase was used to avoid overloading. When the 3-4-monol peak was detected, the exit gases were bubbled through 5-methylnonane (25 mg.). The solution so obtained was transferred to a sodium chloride microcell (0·133 mm.), and the

thickness of a variable space cell filled with 5-methylnonane and adjusted to eliminate the 13·7 μ band due to the hydrocarbon. The optical densities of the mixtures at 12·9 and 13·46 μ were measured with a Perkin-Elmer Model 21 infrared spectrometer fitted with a sodium chloride prism, and were used to determine the 4- and 3-alcohol concentrations by differential analysis. The extinction coefficients of the two pure alcohols at these wavelengths were determined at various concentrations in 5-methylnonane. Results with artificial mixtures were:

	Mixture I		Mixture II		Mixture III	
Isomer	Calc. (%)	Found (%)	Calc. (%)	Found (%)	Calc. (%)	Found (%)
3-ol	42	40	48	46	35	34
4-ol	58	60	52	54	65	66

Conversion of the Diols into Monols.—The diol mixture (20 mg.) obtained by distillation and partition chromatography was shaken with concentrated hydrochloric acid for 20 min., then extracted with purified pentane. Evaporation of the dried (Na_2SO_4) extract yielded the chloro-alcohols, the infrared spectrum of which, compared with that of the diols, showed a decrease in the hydroxyl absorption at 3·0 μ and a new absorption at 13·3 μ due to the C–Cl stretching vibration.

Hydrogenation of the chloro-alcohols with 2% palladium–calcium carbonate (0·2 g.) in methanol (5 ml.) yielded monols, which did not show an absorption at 13·3 μ. On chromatography no diols were detected, but the 2,5-diol was lost when this procedure was used.

5-Methylnonan-5-ol.—This alcohol, prepared as described by Whitmore and Woodburn,[16] had b. p. 103—104°/24 mm., n_D^{25} 1·4328 (Found: active H, 0·61. Calc. for $C_{10}H_{21}OH$: active H, 0·63%).

5-Methylnonane.—5-Methylnonan-5-ol (500 g.) was slowly distilled from iodine (0·1 g.) at atmospheric pressure. The distillate was dried ($CaCl_2$) and redistilled to yield 5-methylnon-4-ene, b. p. 155—156°/655 mm. (380 g.) (Found: I val., 180. Calc. for $C_{10}H_{20}$: I val., 180). Hydrogenation of 5-methylnon-4-ene, at 100°/150 lb./in.^{2} in the presence of 2% palladium–calcium carbonate, and fractionation of the product (column " A "), yielded pure 5-methylnonane,[17] b. p. 160°/655 mm., n_D^{21} 1·4122 [Found: C, 84·6; H, 15·5. Calc. for $C_{10}H_{22}$: C, 84·4; H, 15·6%; I val. (Wijs 1 hr.), <1]. The 5-methylnonane in oxidation experiments gave no reaction with ferrous thiocyanate, when tested qualitatively for peroxides.

5-Methylnonan-4-ol.—5-Methylnonan-4-one, prepared from 2-methylhexanoyl chloride [18] and propyl bromide by the modified Grignard reaction of Percival *et al.*,[19] was reduced with lithium aluminium hydride. The product, after distillation (column " B ") and chromatography on alumina from pentane, yielded pure 5-methylnonan-4-ol,[20] b. p. 197·8—198·0°/654 mm., n_D^{25} 1·4340, n_D^{30} 1·4320 (Found: C, 75·8; H, 13·9. Calc. for $C_{10}H_{22}O$: C, 75·9; H, 14·0%).

5-Methylnonan-3-ol.—5-Methylnonan-3-one (b. p. 194—196°/655 mm.), prepared from 3-methylheptanoyl chloride [21] and ethyl bromide, gave as above *5-methylnonan-3-ol*, b. p. 197·5—197·6°/655 mm., n_D^{26} 1·4326, n_D^{30} 1·4312 (Found: C, 75·9; H, 13·7. $C_{10}H_{22}O$ requires C, 75·9; H, 14·0%).

5-Methylnonan-2-ol.—5-Methylnonan-2-one, prepared similarly from 1-bromo-3-methylheptane [22] and acetyl chloride, yielded similarly *5-methylnonan-2-ol*, b. p. 202·0—202·1°/655 mm., n_D^{25} 1·4320, n_D^{30} 1·4312 (Found: C, 76·0; H, 14·5. $C_{10}H_{22}O$ requires C, 75·9; H, 14·0%).

5-Methylnonan-1-ol.—Methyl hydrogen succinate (66 g.; m. p. 58°), 3-methylheptanoic acid (21 g.), and sodium (0·35 g.), in methanol (300 c.c.), were electrolysed as described by Linstead *et al.*[21] The product was distilled and the mixture, b. p. 132—142°/60 mm. (28·5 g.), of methyl 5-methylnonanoate and dimethyl adipate was reduced with lithium aluminium hydride. The ether layer, after addition of dilute acid, was washed with water to extract most of the hexane-1,6-diol. The ether extract was distilled and the fraction of b. p. 213·6—216°/654 mm. (2·2 g.) was chromatographed on alumina to yield 5,8-dimethyldodecane (0·9 g.,

[16] Whitmore and Woodburn, *J. Amer. Chem. Soc.*, 1933, **55**, 361.
[17] Calingaert and Soroos, *ibid.*, 1936, **58**, 636.
[18] Levene and Mikeska, *J. Biol. Chem.*, 1929, **84**, 571.
[19] Percival, Wagner, and Cook, *J. Amer. Chem. Soc.*, 1953, **75**, 3731.
[20] Powell and Nielsen, *ibid.*, 1948, **70**, 3627.
[21] Linstead, Shepard, Weedon, and Lunt, *J.*, 1953, 1538.
[22] Levene and Marker, *J. Biol. Chem.*, 1931, **91**, 93.

eluted with pentane) and *5-methylnonan-1-ol*, n_D^{30} 1·4340 (0·6 g., eluted with ether) (Found: C, 76·1; H, 14·5. $C_{10}H_{22}O$ requires C, 75·9; H, 14·0%).

2-Butylhexan-1-ol.—2-Butylhexanoic acid, b. p. 160—162°/35 mm., n_D^{30} 1·4396, prepared as described by Levene and Cretcher,[23] was reduced with lithium aluminium hydride, and the product distilled (column " B ") and chromatographed on alumina from pentane, to yield *2-butylhexan-1-ol*, b. p. 209·4°/655 mm., n_D^{30} 1·4328 (Found: C, 75·7; H, 14·3. $C_{10}H_{22}O$ requires C, 75·9; H, 14·0%).

5-Methylnonane-2,5-diol.—5-Oxohexan-2-ol [24] (12 g.) was treated with the Grignard derivative of n-butyl bromide (25 g.); the crude diol (10 g.), after distillation and recrystallisation from hexane, afforded *5-methylnonane-2,5-diol*, b. p. 93°/0·25 mm., m. p. 70° (Found: C, 69·0; H, 12·7. $C_{10}H_{22}O_2$ requires C, 68·9; H, 12·7%).

5-Methylnonane-3,5-diol.—5-Oxohexan-2-ol [25] (22 g.) with the Grignard derivative of n-butyl bromide (60 g.) gave a crude diol (18 g.) which on distillation and chromatography on alumina from pentane, afforded *5-methylnonane-3,5-diol*, b. p. 77·5°/0·1 mm., n_D^{30} 1·4407 (Found: C, 68·7; H, 12·9. $C_{10}H_{22}O_2$ requires C, 68·9; H, 12·7%).

5-Methylnonane-4,5-diol.—5-Methylnonan-4-ene (7 g.) was hydroxylated, following the procedure of Swern *et al.*,[26] with hydrogen peroxide (4 g., 130-vol.) and 98—100% formic acid (51 c.c.) for 20 hr. at 40°. The product, distilled and chromatographed on alumina from pentane, afforded *5-methylnonane-4,5-diol*, b. p. 86°/0·5 mm., n_D^{30} 1·4463 (Found: C, 68·7; H, 12·4%).

The authors are grateful to Dr. J. R. Nunn and Professor F. L. Warren for their interest, and Dr. V. Pretorius for assistance with the development of the flame detector.

National Chemical Research Laboratory,
South African Council for Scientific and Industrial Research,
Pretoria, S. Africa. [*Received, April 20th*, 1959.]

[23] Levene and Cretcher, *ibid.*, 1918, **33**, 508.
[24] Adams and Vander Werf, *J. Amer. Chem. Soc.*, 1950, **72**, 4368.
[25] Bergman and Resnik, *J. Org. Chem.*, 1952, **71**, 1292.
[26] Swern, Billen, and Scanlan, *J. Amer. Chem. Soc.*, 1946, **68**, 1504.

---

663. *Studies of* Aspergillus niger. *Part XI.* Enzymic Synthesis of a Pseudoaldobiuronic Acid.*

By S. A. Barker, A. Gómez-Sánchez, and M. Stacey.

Two acidic oligosaccharides produced when *A. niger* " 152 " was grown in a medium containing maltose and D-glucurone as the sole sources of carbon have been characterised as 2-*O*-α-D-glucopyranosyl-D-glucuronic acid and *O*-α-D-glucopyranosyl-(1→6)-*O*-α-D-glucopyranosyl-(1→2)-D-glucuronic acid.

Previous studies [1] have shown that *Aspergillus niger* " 152 " contains a transglucosylase capable of synthesising isomaltose and panose [*O*-α-D-glucopyranosyl-(1→6)-*O*-α-D-glucopyranosyl-(1→4)-D-glucose] from maltose. In the present communication D-glucuronic acid has been used as an alternative acceptor to synthesise enzymically a pseudoaldobiuronic acid, *i.e.*, a glycosylglycuronic acid.. Whereas many aldobiuronic acids (*i.e.*, the isomeric compounds in which the glycuronic acid is the non-reducing moiety) have been obtained as acid-stable hydrolysis products of acidic polysaccharides (*e.g.*, cellobiuronic acid from Type III *Pneumococcus* polysaccharide [2]) the relatively acid-labile pseudoaldobiuronic acids have not been so isolated.

When *Aspergillus niger* " 152 " was grown in a medium containing maltose and D-glucurone, oligosaccharides of both the acidic and the neutral type were detected after 60—70 hr. After 150 hr. the mixture of suggars was fractionated on a charcoal–Celite

* Part X, *J.*, 1958, 2583.

[1] Barker and Carrington, *J.*, 1953, 3588.
[2] Reeves and Goebel, *J. Biol. Chem.*, 1941, **139**, 511.

column [3] by gradient elution with aqueous ethanol.[4] After further purification of certain fractions by passage down Deacidite FF (CO_3^{2-}) resin, two chromatographically pure compounds, A and B, were obtained. On the assumption that oxidation with hypoiodite was quantitative,[5] the molecular weight of compound A was 376 (the sodium salt of a pseudoaldobiuronic acid $C_{12}H_{19}O_{12}Na$ requires 378). Under similar conditions the molecular weight of compound B was 518 (the trisaccharide $C_{18}H_{29}O_{17}Na$ requires 540).

Acidic hydrolysis of compound A gave only D-glucose (characterised as *N*-*p*-nitrophenyl β-D-glucopyranosylamine) and D-glucuronic acid (characterised as *N*-*p*-nitrophenyl D-glucuronosylamine). Uronic acid determination [6] showed that a mole of hexuronic acid was contained in 379 g. of compound A; thus the disaccharide contained only one hexuronic acid moiety. The infrared spectra of compound A confirmed the presence of a carboxylic acid group. The sequence of sugar units was determined by oxidation of compound A with hypoiodite and subsequent acid-hydrolysis. Only glucose (characterised as D-glucosazone) and D-glucosaccharic acid (identified by paper ionophoresis in 0·2M-acetate buffer, pH 5) were detected in the hydrolysate, indicating that compound A was a glucosylglucuronic acid. The acid-lability of compound A also indicated this sequence. The high optical rotation ($[\alpha]_D$ +89°) and the infrared spectrum [7] of compound A [type 2a absorption at 852 (Na salt) and 845 cm.$^{-1}$ (free acid)], both indicated an α-glycosidic linkage. Absorption peaks at 919 and 775 cm.$^{-1}$ corresponding to type 1 and type 3 absorption of a pyranose ring were also present.

Preliminary examination suggested the presence of a 1⟶2 linkage in compound A since, like 2-*O*-α-D-glucopyranosyl-D-glucose (kojibiose) and sophorose, this substance did not react with alkaline triphenyltetrazolium chloride [8] under conditions in which D-glucuronic acid, D-glucose, nigerose, maltose, and isomaltose did. A 1⟶2 linkage was also indicated by the low reducing power (56·2% of that calculated for a disaccharide of molecular weight 378) with the cuprimetric Shaffer–Hartmann reagent [9] and its stoicheiometric reaction with alkaline hypoiodite.[5] Compound A was esterified with diazomethane, and the methyl ester then reduced with sodium borohydride. The neutral disaccharide alcohol produced had $[\alpha]_D$ +81°, in confirmation of the assignment of an α-linkage. The alcohol consumed 4·5 mol. of periodate, liberating 2·85 mol. of formic acid and 0·95 mol. of formaldehyde. The theoretical values for 2-*O*-α-D-glucopyranosyl-D-sorbitol are 5, 3, and 1 respectively. As final confirmation of the 1⟶2 linkage, compound A was reduced to kojibiose by a method similar to that applied by Jones and Reid: [10] compound A was converted into its diethyl orthoformate by treatment with triethyl orthoformate and hydrochloric acid and then esterified with diazomethane; reduction of the product with lithium aluminium hydride and removal of the diethyl orthoformate by warm dilute acid afforded a neutral disaccharide. This disaccharide was characterised as kojibiose by (i) its low mobility M_G 0·30 on ionophoresis in borate buffer, (ii) its high optical rotation, $[\alpha]_D$ +121°, (iii) its low reducing power (15·5% of that calculated for a disaccharide) with the Shaffer–Hartmann reagent,[9] (iv) its failure to react with alkaline triphenyltetrazolium chloride,[8] and (v) its almost stoicheiometric reaction (89%) with alkaline hypoiodite.[5] From the above evidence compound A is 2-*O*-α-D-glucopyranosyl-D-glucuronic acid.

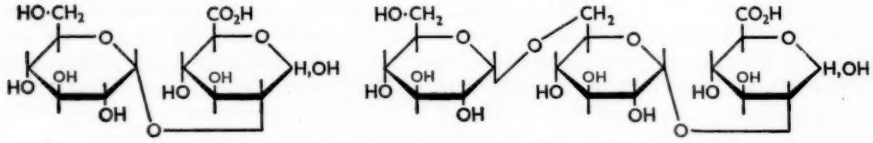
The high optical rotation ($[\alpha]_D$ +110°) and infrared spectrum of compound B (type 2a absorption [7] at 835 cm.$^{-1}$; no β-glycosidic absorption at 890 cm.$^{-1}$) indicated that both the glucosidic linkages in this trisaccharide had the α-configuration. The infrared spectrum also showed the presence of a carboxylic acid group (C=O stretching, 1615 cm.$^{-1}$). Partial

[3] Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677.
[4] Alm, Williams, and Tiselius, *Acta Chem. Scand.*, 1952, **6**, 826.
[5] Hirst, Hough, and Jones, *J.*, 1949, 928.
[6] Barker, Foster, Siddiqui, and Stacey, *Talanta*, 1958, **1**, 216.
[7] Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171.
[8] Feingold, Avigad, and Hestrin, *Biochem. J.*, 1956, **64**, 351.
[9] Shaffer and Hartmann, *J. Biol. Chem.*, 1921, **45**, 377.
[10] Jones and Reid, *J.*, 1955, 1890.

XUM

hydrolysis of compound B liberated glucose, glucuronic acid, isomaltose, and compound A. The sequence of sugar units was determined by oxidation of compound B with hypoiodite and subsequent hydrolysis, the products being glucose, isomaltose, glucosaccharic acid, and a non-reducing acidic disaccharide; no glucuronic acid, gluconic acid or reducing acidic disaccharide was detected. On this evidence compound B was tentatively assigned the structure *O*-α-D-glucopyranosyl-(1→6)-*O*-α-D-glucopyranosyl-(1→2)-D-glucuronic acid (2-*O*-α-isomaltosyl-D-glucuronic acid).

Compound A *Compound B*



The structures of compounds A and B suggest that the *A. niger* transglucosylase responsible for the synthesis of panose from maltose also synthesised compounds A and B. In this it would resemble closely the transglucosylase obtained from *Betacoccus arabinosaceous* [11] which synthesised panose from a sucrose–maltose mixture but elaborated *O*-β-D-galactopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→2)-D-glucose in a sucrose–lactose medium.

Experimental

Growth of Aspergillus niger " 152 " *on a Medium containing Maltose-D-glucurone.*—Medium (1 l.) was prepared containing ammonium nitrate (2·5 g.), potassium dihydrogen phosphate (1·0 g.), magnesium sulphate heptahydrate (0·25 g.), ferrous sulphate heptahydrate (0·05 g.), zinc sulphate heptahydrate (0·05 g.), N-hydrochloric acid (1 c.c.), maltose hydrate (20 g.), and D-glucurone (20 g.). Erlenmeyer flasks, each containing this medium (50 c.c.), were autoclaved at 15 lb./sq. in. for 20 min., cooled, inoculated with *Aspergillus niger* " 152 " from malt–agar slopes, and incubated at 30°. Aliquot parts (25 μl.), removed under sterile conditions, were analysed by paper ionophoresis in an acetate buffer (pH 5·0), and by paper chromatography with butanol–acetic acid–water (4 : 1 : 5). After 70 hr., a reducing acidic compound, which moved more slowly than D-glucuronic acid on the ionophoretogram, was detected, its concentration increasing to a maximum at 125 hr. After 150 hr., when most of the maltose had been consumed, the culture filtrate and water washings (3 × 50 c.c.) of the mycelium were neutralised, boiled for 10 min. to arrest enzyme action, and cooled. After addition of N-sodium hydroxide until a constant pH of 8·0 was attained, the solution was concentrated *in vacuo* below 40°. Paper ionophoresis (as above) revealed the presence of D-glucuronic acid, two additional acidic compounds (compound A, $M_{\text{glucuronic acid}}$ 0·72; compound B, $M_{\text{glucuronic acid}}$ 0·57; both stained red-brown by aniline hydrogen phthalate [12]), and neutral components. Paper-chromatography (as above) revealed D-glucuronic acid, D-glucose, maltose and at least five oligosaccharides. The solution was freeze-dried (17 g.).

Fractionation of the Mixture.—The mixture (17 g.) in water (150 c.c.) was introduced on to a charcoal–Celite column (length 45 cm.; diameter 6 cm.). Washing with water eluted successively fractions I (350 c.c.; sodium D-glucuronate), II [500 c.c.; sodium D-glucuronate, D-glucose (5·1 g.)], III [600 c.c.; mainly compound A (0·30 g.)], IV [800 c.c.; compound A (0·20 g.)] and V [1700 c.c.; compound A (0·36 g.)]. Gradient elution with 0→5% aqueous ethanol afforded further pure compound A (VI 0·34 g. in 4050 c.c.) and fractions VII (900 c.c.; compound A and neutral oligosaccharides; 0·17 g.) and VIII (150 c.c.; compound A, neutral oligosaccharides, compound B; 0·05 g.). Gradient elution with 5→10% aqueous ethanol eluted the remaining compound B together with neutral oligosaccharides (IX; 0·31 g. in 1600 c.c.) and fraction X (1800 c.c.; neutral oligosaccharides 0·99 g.). Fraction IX (0·28 g.) in water (60 c.c.) was stirred for 24 hr. with Deacidite FF (carbonate form; 12 g.), then packed in a column, and the resin was washed with water. The freeze-dried aqueous eluate yielded

[11] Bailey, Barker, Bourne, Grant, and Stacey, *J.*, 1958, 1895.
[12] Partridge, *Nature*, 1949, **164**, 443.

0·158 g. of neutral oligosaccharides. Elution with N-ammonium carbonate (500 c.c.), treatment of the eluate with Zeo-Karb 225 (H^+), and freeze-drying afforded pure compound B (0·105 g.). Compound A (free acid) was recovered from fraction VII by using the same procedure.

Characterisation of Compound A.—(i) *Optical measurements.* Compound A (sodium salt from IV and VI) was a white hygroscopic powder, having $[\alpha]_D^{18}$ 89·0° (*c* 2 in H_2O). Its infrared spectrum showed peaks ($cm.^{-1}$) at 3380, 2915, 2340, 2115, 1617, 1565, 1545, 1512, 1420, 1362, 1311, 1260, 1207, 1162, 1145, 1050, 955, 919, 852, 775, 670. Compound A (free acid from VII) showed infrared absorption peaks at 3380, 2910, 2330, 2105, 1782, 1645, 1527, 1420, 1355, 1265, 1207, 1155, 1055, 919, 845, and 780 $cm.^{-1}$.

(ii) *Paper chromatography.* Compound A moved as a single component $R_{glucose}$ 0·34 in butanol–acetic acid–water (4 : 1 : 5) and 0·47 in ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4). It could be detected with aniline hydrogen phthalate [12] or silver nitrate–sodium hydroxide,[13] but not with alkaline triphenyltetrazolium chloride.[8]

(iii) *Products of acidic hydrolysis.* Compound A (sodium salt; 50 mg.) was dissolved in 1·5N-sulphuric acid (6 c.c.) and divided into three 2 c.c. portions which were heated at 100° for 1, 2, and 3 hr. severally. Paper chromatography (as above) of the neutralised (barium carbonate) hydrolysates showed only glucose and glucuronic acid in all three hydrolysates. These were combined, concentrated *in vacuo* (40°), and separated into bands on two sheets of Whatman No. 1 paper (46 × 57 cm.) irrigated with butanol–acetic acid–water (4 : 1 : 5) for 3 days.

The strip containing the glucose was eluted and the solution concentrated to a syrup (12·6 mg.). Refluxing this for 15 min. with an aliquot part (0·5 c.c.) of a solution containing *p*-nitroaniline (9 g.), methanol (200 c.c.), and concentated hydrochloric acid (0·14 c.c.) yielded *N*-*p*-nitrophenyl β-D-glucopyranosylamine dihydrate (6·1 mg.). Recrystallisation from methanol yielded pale yellow needles, m. p. and mixed m. p. 184°.

The strip containing the barium glucuronate was eluted, the solution treated with Amberlite I.R.-120 (H^+) to remove barium ions, and concentrated to a syrup (12·8 mg.). Repeated evaporation with methanol and heating for 3 hr. at 40—50° *in vacuo* afforded syrupy glucuronolactone which was treated with *p*-nitroaniline (10 mg.) and methanol containing 0·01% of hydrochloric acid till a clear solution was obtained. After 15 minutes' heating, the solvent was evaporated, and the residue was treated with ether and some spots of methanol and recrystallised to give *N*-*p*-nitrophenyl D-glucuronosylamine, m. p. and mixed m. p. 128—130°. Hamilton, Spriesterbach, and Smith [14] quote m. p. 129—130°.

(iv) *Uronic acid content.* As determined by the method of Barker, Foster, Siddiqui, and Stacey,[6] the weight (g.) of compound A containing one mole of glucuronic acid was 379 ($C_{12}H_{19}O_{12}Na$ requires 378).

(v) *Oxidation by hypoiodite and copper-reducing value.* Under conditions in which maltose was oxidised stoicheiometrically by iodine in alkaline solution (Hirst, Hough, and Jones [5]) compound A, in two determinations, consumed the amount of iodine expected of a reducing disaccharide of molecular weight 376·5 (average of 370 and 383). When analysed by the Shaffer–Hartmann method,[9] compound A (0·965 mg.) had a reducing power equivalent to 0·52 mg. of maltose monohydrate. This corresponded to 56·2% of the calculated value for a disaccharide of molecular weight 378.

(vi) *Hydrolysis of hypoiodite-oxidation product.* Compound A (19 mg.) in water (36 c.c.) was treated with 0·1N-iodine (7·2 c.c.) and a solution (15 c.c.) containing 0·2M-sodium hydrogen carbonate and 0·2M-sodium carbonate. After 2 hr. at room temperature an excess of 30% formaldehyde solution was added and, after 1 hr., the solution was freeze-dried. The residue was dissolved in water and treated with an excess of Amberlite I.R.-120 (H^+). The eluate was neutralised with silver carbonate, concentrated by freeze-drying, then again passed down a column of Amberlite I.R.-120 (H^+). The products (12·4 mg.) obtained by freeze-drying of the eluate were analysed by ionophoresis in 0·2M-acetate buffer (pH 5·0). Non-reducing components were detected with $M_{glucuronic\ acid}$ 0 (weak), 0·97 (weak), and 1·23 (strong). After neutralisation with 0·25N-sodium hydroxide only the component with *M* 1·23 was detected. Oxidised compound A was hydrolysed with 2N-hydrochloric acid at 100° for 2 hr., the hydrochloric acid removed with methyl di-n-octylamine, and the aqueous solution stirred with Deacidite FF (CO_3^{2-}) (0·7 g.) for 20 hr. Elution with water afforded D-glucose (6·8 mg.) which

[13] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.
[14] Hamilton, Spriesterbach, and Smith, *J. Amer. Chem. Soc.*, 1957, **79**, 443.

on being heated for 20 min. at 90° with phenylhydrazine (0·2 c.c.) in 40% acetic acid (1·7 c.c.) gave D-glucosazone, m. p. and mixed m. p. 196—198° (decomp.). The resin was eluted with N-ammonium carbonate (35 c.c.), the eluate treated with Zeo-Karb 225 (H^+), carbon dioxide removed, a few drops of ammonia added, and the solution freeze-dried. Paper-ionophoretic analysis showed that the residue (7·9 mg.) contained only a single compound with the mobility of dipotassium glucosaccharate.

(vii) *Reduction of compound A to* 2-O-α-D-*glucopyranosyl*-D-*glucose.* Compound A (0·38 g.), triethyl orthoformate (10 c.c.), and concentrated hydrochloric acid (0·07 c.c.) were shaken at room temperature for 36 hr. Whenever the suspension became neutral additional amounts of the acid (not exceeding 0·1 c.c. each time) were added up to a total of 0·45 c.c. The mixture was centrifuged, the residue washed with triethyl orthoformate (2 × 25 c.c.), and the supernatant liquid and washings were combined, treated with an excess of diazomethane in ether, and after several hours concentrated *in vacuo* at 40°. The residue was repeatedly dissolved in ethanol, and the solution concentrated to ensure removal of triethyl orthoformate. A solution of the orthoformate derivative of the methyl ester of compound A in dry peroxide-free dioxan (10 c.c.) was stirred for 24 hr. with lithium aluminium hydride (0·3 g.) in dioxan (300 c.c.). The excess of hydride was then destroyed by addition of ethyl acetate (10 c.c.) and afterwards of water (10 c.c.). The filtrate and washings were concentrated *in vacuo* at 40°, and the residue was dissolved in water and freeze-dried (423 mg.). Extraction with acetone and subsequent evaporation gave a syrup (261 mg.) which contained only one non-reducing component, which had $R_{glucose}$ 1·1 in ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4). This orthoformate derivative (260 mg.) was hydrolysed with 0·1N-hydrochloric acid (10 c.c.) at room temperature for 4 days and then at 60° for 5 hr. Paper chromatography in the solvent just mentioned showed components with the mobilities of a disaccharide and glucose. The disaccharide (32·5 mg.) was recovered by streaking the mixture across 8 sheets of Whatman No. 1 paper (46 × 57 cm.), irrigating it with butan-1-ol–ethanol–water–ammonia (40 : 10 : 49 : 1), and eluting the strips containing the disaccharide.

The disaccharide had $[\alpha]_D$ +121° (*c* 0·15 in H_2O) and could be detected on chromatograms with aniline hydrogen phthalate [12] and alkaline silver nitrate [13] but not with triphenyltetrazolium chloride [8]. In the butanol–ethanol–water–ammonia solvent it had $R_{glucose}$ 0·44 and in 0·2M-borate buffer (pH 10) had M_G 0·30. In all these characteristics it was identical with 2-*O*-α-D-glucopyranosyl-D-glucose separated on the same chromatogram. Ionophoresis in 0·2M-acetate buffer of pH 5·0 showed that the disaccharide was neutral and free from acidic impurities. When oxidised by alkaline hypoiodite [5] the disaccharide (2·8 mg.) consumed iodine equivalent to 2·5 mg. of maltose (89% of the theoretical value for a disaccharide). When analysed by the cuprimetric Shaffer–Hartmann reagent,[9] the disaccharide (5·6 mg.) had a reducing power equivalent to 0·87 mg. of maltose hydrate (15·5% of the expected value for a disaccharide, a stoicheiometric reaction being assumed).

(viii) *Reduction of compound* A *to* 2-O-α-D-*glucopyranosyl*-D-*sorbitol.* Compound A (free acid; 190 mg.) in methanol (25 c.c.) was esterified with an excess of diazomethane in ether. The solution was concentrated *in vacuo* at 40°. The residue, dissolved in water (15 c.c.), was added dropwise to sodium borohydride (200 mg.) in water (20 c.c.). After 12 hr. at 18° the excess of hydride was destroyed, Amberlite I.R.-120 (H^+) (10 c.c.) added, and the solution freeze-dried. After removal of boric acid as methyl borate, the freeze-dried residue weighed 123·4 mg. Paper ionophoresis in 0·2M-acetate buffer (pH 5·0) revealed reducing components but showed that the major neutral component was accompanied by some acidic components. These were removed by absorption on Deacidite FF (CO_3^{2-}), and the neutral disaccharide alcohol (45·9 mg.) was recovered by freeze-drying.

The disaccharide alcohol had $[\alpha]_D^{21}$ +81° (*c* 0·3 in water) and moved as a single non-reducing component having $R_{glucose}$ 0·41 in butanol–ethanol–water–ammonia (40 : 10 : 49 : 1) and M_G 0·26 in 0·2M-borate buffer (pH 10). On treatment of the disaccharide alcohol (15 mg.) with 0·04M-sodium periodate (50 ml.) in the dark at room temperature, periodate consumption was 4·4 (4 hr.), 4·5 (14 hr.) and 4·5 (18 hr.) mol. After 18 hr., 2·85 mol. of formic acid were produced and 0·95 mol. of formaldehyde [15] was liberated.

Characterisation of Compound B.—(i) *Optical measurements.* Compound B (sodium salt) had $[\alpha]_D^{19}$ +110° (*c* 0·07 in water). Its infrared spectrum showed peaks ($cm.^{-1}$) at 3420, 2940, 2380, 1615, 1420, 1150, 1110, 1050, 955, 920, 835, and 765.

[15] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.

(ii) *Paper chromatography.* Compound B moved as a single component of $R_{glucose}$ 0·13 in butanol–acetic acid–water (4 : 1 : 5) and could be detected with aniline hydrogen phthalate [12] and alkaline silver nitrate.[13]

(iii) *Products of partial acid-hydrolysis.* Compound B (14 mg.) was hydrolysed with N-sulphuric acid (7·5 c.c.) at 80—90° for 1 hr. After neutralisation with barium carbonate the solution was freeze-dried (17·5 mg.). Paper ionophoresis in 0·2M-acetate buffer of pH 5·0 showed the presence of neutral compounds, unchanged compound B, an acidic oligosaccharide with the same mobility as compound A, and D-glucuronic acid. Paper ionophoresis in 0·2M-borate buffer (pH 10·0) showed the presence of D-glucuronic acid, D-glucose, compound A, compound B, and probably a disaccharide with the mobility of isomaltose partially overlapping compound B. Paper-chromatographic analysis in butan-1-ol–ethanol–water–ammonia (40 : 10 : 49 : 1) showed D-glucose and isomaltose in addition to three acid compounds near the starting line. The hydrolysate was shaken with Deacidite FF (CO_3^{2-}) (1 g.) for 24 hr., and the filtrate was freeze-dried. Ionophoresis of the residue (5·7 mg.) in 2M-borate buffer (pH 10·0) confirmed that the only neutral compounds present were glucose and isomaltose.

(iv) *Oxidation by hypoiodite.* When oxidised [5] with iodine in alkaline solution, compound B consumed the amount of iodine expected of a reducing trisaccharide of molecular weight 518 (Calc. for $C_{18}H_{29}O_{17}Na$: 540).

(v) *Hydrolysis of hypoiodite-oxidation products.* Compound B (35 mg.) in water (100 c.c.) was mixed with 0·1N-iodine (20 c.c.) and a solution (40 c.c.) containing 0·2M-sodium carbonate and 0·2M-sodium bicarbonate added. After 2 hr., ions, etc., were removed as for compound A, and the oxidised compound B (16 m.) was obtained as a single non-reducing component with $M_{glucuronic\ acid}$ 0·95 in 0·2M-acetate buffer (pH 5·0) detectable with alkaline silver nitrate.[13] The oxidation product was hydrolysed with N-sulphuric acid (2 c.c.) at 90° for 1 hr., and the solution neutralised as above and freeze-dried (17 mg.). Paper ionophoresis in 0·2M-acetate buffer (pH 5·0) showed the presence of reducing neutral components detectable with both aniline hydrogen phthalate [12] and alkaline silver nitrate,[13] and two acidic components only detectable with the latter reagent. One of the acidic components had the same mobility as D-glucosaccharic acid. Paper chromatography in butan-1-ol–acetic acid–water (4 : 1 : 5) showed the presence of, *inter alia*, glucose and isomaltose. No D-glucuronic acid or D-gluconic acid was detected.

One of us (A. G. S.) thanks the British Council for the award of a Scholarship.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, May 6th,* 1959.]

---

664. *Structure and Reactivity of the Oxyanions of Transition Metals. Part VI.* Photolysis of Chromate, Permanganate, and Related Compounds in Rigid Media at Low Temperatures.*

By U. KLÄNING and M. C. R. SYMONS.

Rigid solutions of permanganate in a variety of solvents at 77° K are readily photolysed by 3650 or 2537 Å light to give tervalent manganese and oxygen. Alcoholic solvents are not attacked to any extent and it is concluded, by comparison with the behaviour of chlorine dioxide, that free oxygen atoms are not involved in the photolysis.

Other tetrahedral oxyanions, including manganate, hypomanganate, chromate, and vanadate do not decompose under similar conditions.

When studying photolysis it may be informative to use a medium whose rigidity is sufficient to prevent migration of some, or all, of the molecular or ionic fragments resulting from

* Part V, *J.*, 1959, 829.

XUM

bond fission.[1,2,3,4] Under such conditions chain decompositions cannot occur and chemically unstable intermediates may become permanently trapped and react further only when the glass softens. These intermediates can be studied spectrophotometrically or magnetically in the glass, and the course of reaction can often be deduced by analysis of the products formed on warming to room temperature.

Spectrophotometric and magnetic studies of several oxyanions of the transition metals have given a fairly detailed picture of the ground and first excited states of these ions.[5] Studies of reactivity, which have been confined to simple electron- and proton-transfer reactions, are now extended to photolyses, and the results are considered in the light of the structural studies.

An extensive study of the photolysis of permanganate was made by Zimmerman [6] who measured quantum yields between 2537 and 5780 Å for aqueous permanganate in the pH range 6·8 to 13. The quantum yield of oxygen formation, ϕ, was independent of pH and light intensity, but strongly dependent upon wavelength and, in the visible region, slightly upon temperature. At all wavelengths ϕ was small compared with unity.

Zimmerman [6] also studied the isotopic content of oxygen evolved from solutions in water enriched with $H_2{}^{18}O$ and found that all the oxygen was derived from permanganate. From these results, and a consideration of the energetics of various mechanisms, he concluded that by far the most probable route for oxygen formation was

$$MnO_4^- + h\nu \longrightarrow MnO_3^- + O_2 \quad \ldots\ldots\ldots\ldots (I)$$

The small quantum yields were explained by the postulate that rapid internal conversion of excited permanganate ions gave ions in the ground state which possessed excess of vibrational energy. These could then dissociate thermally or lose energy to the solvent.

Bowen and his co-workers [7] found no photodecomposition for chromate or acid chromate ions exposed to light of wavelength greater than 3000 Å. Alkyl chromates, however, are rapidly photolysed with 3650 Å light.[8]

Experimental

Materials.—Water was distilled from alkaline permanganate in a nitrogen atmosphere, and other solvents and reagents were " AnalaR " or purified by standard procedures. It was established that solutions containing permanganate were quite stable during the period required for preparation. The solutions were stored, when necessary, at −70°.

Glasses.—These were prepared as described previously,[2] but phosphoric acid was not added to the alcoholic solvents. Acidic glasses were prepared by using suitable mixtures of water, syrupy phosphoric acid, and sodium hydroxide.

Electron Spin Resonance and Spectrophotometric Measurements.—These were made as described previously.[3]

Photolyses and Analytical Procedures.—Glasses in quartz test tubes were irradiated with a B.T.H. 250 w mercury arc, type ME/D, held externally to a Pyrex Dewar flask containing liquid oxygen or nitrogen and the sample tubes, or with a low-pressure 110 w mercury arc similar to that already described [2] which was immersed directly in the coolant and surrounded by sample tubes.

After warming to room temperature, irradiated permanganate solutions were analysed spectrophotometrically or titrimetrically with ferrous ammonium sulphate. When phosphate glasses were used, the irradiated solutions did not change in appearance on warming, and the

[1] Norman and Porter, *Proc. Roy. Soc.*, 1955, *A*, **230**, 399.
[2] Symons and Townsend, *J.*, 1959, 263.
[3] Gibson, Symons, and Townsend, *J.*, 1959, 269.
[4] Kläning and Symons, *Proc. Chem. Soc.*, 1959, 95.
[5] Cf. *J.*, 1956, 3373, 4710; 1957, 659, and Carrington, Thesis, Southampton, 1959.
[6] Zimmerman, *J. Chem. Phys.*, 1955, **23**, 825.
[7] Bowen and Chatwin, *J.*, 1932, 2081; Bowen and Bunn, *J.*, 1927, 2353.
[8] Kläning, *Acta Chem. Scand.*, 1958, **12**, 807.

resultant spectrum was that expected for manganese(III) in this solvent. A marked evolution of gas was observed on warming. In alcohol, disproportionation of the manganese(III) present in the glass gave manganese(II) and precipitated manganese dioxide. The total oxidizing power was estimated titrimetrically and the results of these experiments are given in Table 1.

For all other oxyions studied, it was established that, after irradiation and warming to room temperature, the visible and ultraviolet spectra had not changed. The results are summarised in Table 1.

TABLE 1. *Details of the photolyses of various oxyanions.*

Ion	$10^3 \times$ Concn. (M)	Medium	Temp. (°K)	Wavelength [a] (Å)	Time (hr.)	Decomposition [b] (%)
MnO_4^-	0·1	Phosphate	90	3650	12	85
,,	3	,,	,,	,,	25	98
,,	2	,,	,,	,,	12	82
,,	,,	,,	,,	,,	18	95
,,	,,	,,	77	2537	36	98
,,	,,	$Me_2CH{\cdot}OH$	90	,,	40	99
MnO_4^{2-}	1	Hydroxide	90	3650	27	0
,,	,,	,,	77	2537	10	0
,,	2	,,	293	3650	6	0
MnO_4^{3-}	1	,,	77	2537	15	0
CrO_4^{2-}	1	Phosphate	,,	,,	12	0
$HCrO_4^-$ [c]	1	,,	,,	,,	12	0

[a] See text for the types of lamp used. [b] Based on conversion into manganese(III) for MnO_4^-. [c] Some $Cr_2O_7^{2-}$ was also present.

No electron spin resonance absorption was detected after prolonged irradiation of permanganate glasses, and a test for acetone after irradiation of a rigid solution of permanganate in isopropyl alcohol showed that very much less than 1 equiv. had been formed. The small quantity detected was probably produced by thermal reactions before and after irradiation.

Photolysis of Chlorine Dioxide.—Some details have already been given.[2] Norman and Porter have shown [1] that in a mixed hydrocarbon glass photolysis is rapid and chlorine monoxide is formed. (They considered the possibility that chlorine dioxide dimerised at 77° K, but our results show conclusively that the monomer is still present as a major component in the unirradiated glass.)

Our results show that in methylcyclohexane the electron spin resonance spectrum due to chlorine dioxide is rapidly lost and a new spectrum consisting of a broad single peak at $g = 2{\cdot}003$ and a shoulder at $g = 2{\cdot}028$ appears. However, in alcoholic solvents the latter spectrum, which is attributed to chlorine monoxide, is superimposed upon a second spectrum with hyperfine lines characteristic of the alcohol radicals.[3] At the same time a violet colour appears, which may also be characteristic of alcohol radicals.[2]

DISCUSSION

Photolysis of Permanganate.—The relevant results are (i) that photolysis proceeds readily to manganese(III) but no further, (ii) that no alcohol radicals are trapped in the glass, and (iii) that photolysis proceeds readily even in inert glasses. These results should be compared with those for chlorine dioxide. On photolysis chlorine monoxide was formed but in solvent alcohol, an equivalent number of alcohol radicals were formed concurrently.

The available primary steps are (1) together with

$$MnO_4^- + h\nu \longrightarrow MnO_3 + O^{\cdot -} \quad \ldots\ldots\ldots\ldots (2)$$

$$MnO_4^- + h\nu \longrightarrow MnO_3^- + O \quad \ldots\ldots\ldots\ldots (3)$$

$$MnO_4^- + h\nu \longrightarrow MnO_2 + O_2^{\cdot -} \quad \ldots\ldots\ldots\ldots (4)$$

Of these, (2) represents the usual mode of bond fission, after excitation, namely, homolysis. Whilst it is conceivable that MnO_3 would undergo further photolysis, there can be little doubt that $O^{\cdot -}$, which is the conjugate acid of $\cdot OH$, would readily attack isopropyl alcohol, the resulting radicals ($Me_2\dot{C}OH$) becoming trapped.[3] Similar arguments apply

to step (3). The results obtained with chlorine dioxide show that oxygen atoms can extract hydrogen from alcohols under these conditions. It is conceivable, but unlikely, that the primary dark back-reaction

$$O + MnO_3^- \longrightarrow MnO_2^- + O_2 \quad \ldots\ldots\ldots\ldots \quad (5)$$

can compete so efficiently that reaction with solvent is eliminated. Step (4) has nothing to commend it. Although MnO_2 is stable when polymeric, the monomer is unknown, and would certainly be extremely reactive.[9] Also, the electron resonance spectrum of the superoxide ion is quite characteristic.[10]

We conclude that reaction (1) is correct. Such a reaction, involving heterolysis of two bonds, is not often met in the field of photochemistry.

Other Oxyanions.—The stability of chromate under these conditions is not surprising since it is far less chemically reactive than permanganate. However, our failure to photolyse either manganate or hypomanganate is remarkable. Hypomanganate, in particular, is generally considered to be extremely unstable and both ions readily disproportionate. However, this instability is thought to be a function of the protonated ions [5] and is not observed in strongly alkaline media.[11] Some relevant thermodynamic constants are in Table 2.

TABLE 2. *Some thermodynamic data for oxyanions (kcal./mole).*

	MnO_4^- [a]	MnO_4^{2-} [a]	MnO_4^{3-} [a]	CrO_4^{2-} [b]	$HCrO_4^-$
$\Delta F°$	−107·4	−120·3	−127·0	−176·1	−184·9
$\Delta H°$	−129·7	−160·5	−185·8 [c]	−213·8	−220·2

[a] Taken from ref. 11. [b] Latimer, "The Oxidation States of the Elements and their Potentials in Aqueous Solutions," Prentice-Hall, Inc., New York, 1952. [c] This value refers to MnO_4^{3-} in concentrated aqueous potassium hydroxide.

A consideration of the structure of the ions MnO_4^-, MnO_4^{2-}, and MnO_4^{3-} might shed light on the problem. Manganate and hypomanganate are thought to have one and two unpaired electrons, respectively, in a doubly degenerate antibonding π-orbital of symmetry *e*. This orbital, which may be pictured as being constructed from filled p–π oxygen orbitals and the d_{z^2} and $d_{x^2-y^2}$ orbitals of manganese is the antibonding analogue of an *e* bonding orbital. In particular, such overlap may tend to link adjacent oxygen atoms weakly, so that the extrusion of an oxygen molecule from a vibrationally excited permanganate ion need not involve free oxygen atoms at any stage. However, in manganate and hypomanganate the presence of electrons in the antibonding *e* level must reduce the effective overall bonding so that the structure will tend towards an extreme in which π-bonding is insignificant. The extrusion of molecular oxygen might then require greater activation energy, as is found experimentally.

Alternatively, if Zimmerman is correct in suggesting that vibrationally excited permanganate ions in the ground state decompose rather than electronically excited ions, then the differences noted may simply be linked to the relative shapes of the configurational co-ordinate curves for the ground and excited states. Other factors which may be important are the greater organisation of solvent molecules by the highly charged ions, and the relative stabilities of the labile ions MnO_2^-, MnO_2^{2-}, and MnO_2^{3-} which must be formed if oxygen molecules are lost by the corresponding tetrahedral ions.

Thanks are offered to the British Council for a grant (to U. K.) and to Dr. D. J. E. Ingram for help relating to electron spin resonance measurements.

DEPARTMENT OF CHEMISTRY, THE UNIVERSITY, SOUTHAMPTON. [*Received, May 8th,* 1959.]

[9] Lott and Symons, *J.*, 1959, 829.
[10] Bennett, Ingram, Symons, George, and Griffith, *Phil. Mag.*, 1955, **46**, 443.
[11] Carrington and Symons, *J.*, 1956, 3373.

665. *Ultraviolet and Infrared Spectra of Some Aromatic Nitro-compounds.*

By C. P. Conduit.

The ultraviolet and infrared spectra of a series of mono-, di-, and tri-nitro-benzenes and -toluenes have been examined and are interpreted in terms of polar and steric effects. The results yield useful structural correlations for the number and position of substituents in polynitro-aromatic compounds.

Spectral characteristics of the nitro-group in aromatic compounds have often been reported. Doub and Vandenbelt [1] examined a number of nitro-compounds but found no correlations with the ultraviolet spectra of other substituted benzenes. Forbes [2] discussed the part played by polar effects in the electronic spectra of mononitrobenzenes, and there is evidence of steric hindrance in alkylnitrobenzenes.[3,4] In the infrared region the asymmetric stretching vibration has been shown to be sensitive to the electronic properties of other substituents,[5,6] and in sterically hindered compounds polarised infrared studies have demonstrated the rotation of the nitro-group out of the plane of the benzene ring.[7] *X*-Ray work confirms this also for some nitroanthracenes.[8]

Little work has been carried out on polynitrobenzenes.[9] In the present investigation the ultraviolet and infrared spectra of the complete isomeric series of di- and tri-nitrobenzenes and -toluenes have been examined to obtain structural correlations in this class of compound. In particular, steric effects were expected to influence the spectra following the recent observations of Wepster and his co-workers.[10]

Experimental

Ultraviolet Spectra.—The compounds were purified by distillation or crystallisation as appropriate. Weighed amounts (15—30 mg.) were dissolved in 50 ml. of absolute ethanol, and 5 ml. of this solution were diluted to 100 ml. with water. The spectra were measured on a Unicam S.P. 500 spectrophotometer in 10 mm. quartz cells against 5% ethanol–water mixture. Cell corrections were applied to all measurements.

Infrared Spectra.—The measurements were made in chloroform (10—30 mg. in 5 ml. of solvent) on a Grubb-Parsons S3A double-beam prism spectrometer. Rock-salt cells of 0·0251 cm. path length were employed. Each spectrum was scanned from 6 to 8 μ at a constant slit width of 0·2 mm. The frequency values obtained are considered to be accurate to ± 2 cm.$^{-1}$.

The integrated intensities were calculated by use of Ramsay's formula $I = (K\Delta\nu/cl) \ln I_0/I_{max.}$, where c = molar concentration, l = path length in cm., $\Delta\nu$ = half-intensity band width in cm.$^{-1}$, $\ln I_0/I_{max.}$ = peak optical density, and K = constant. Ramsay [11] gives values of K for various instrumental conditions but in this work it was taken as 1·56 throughout, the value of $\ln I_0/I_{max.}$ being kept near to 1·2.

In cases where the nitro-group bands were overlapped by others or by splitting of the nitro-frequencies themselves, graphical resolution was employed, and the frequencies, intensities, and band-widths were calculated for the resolved components. The last two quantities are probably correct to $\pm 5\%$.

[1] Doub and Vandenbelt, *J. Amer. Chem. Soc.*, (*a*) 1947, **69**, 2714; (*b*) 1949, **71**, 2412; (*c*) 1955, **77**, 4535.
[2] Forbes, *Canad. J. Chem.*, 1958, **36**, 1350.
[3] Fielding and Le Fèvre, *J.*, 1950, 2812; Brown and Reagan, *J. Amer. Chem. Soc.*, 1947, **69**, 1032; Remington, *ibid.*, 1945, **67**, 1838.
[4] Sherwood and Calvin, *ibid.*, 1942, **64**, 1350.
[5] Brown, *ibid.*, 1955, **77**, 6841.
[6] Kross and Fassel, *ibid.*, 1956, **78**, 4225.
[7] Francel, *ibid.*, 1952, **74**, 1265.
[8] Trotter, *Canad. J. Chem.*, 1959, **37**, 351.
[9] Francke, Hörman, and Schiebe, *Chem. Ber.*, 1957, **90**, 330.
[10] Wepster, *Rec. Trav. chim.*, 1957, **76**, 335; Van Veen, Verkade, and Wepster, *ibid.*, p. 801.
[11] Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 72.

Results

Ultraviolet Spectra.—The absorption curves consisted mainly of a single intense maximum lying in the range 210—280 mμ, with one or more inflexions on the long-wavelength side. For the interpretation of the results it was necessary to identify corresponding bands in the various

Table 1.

Compound	$\lambda_{max.}$ (mμ)	$\nu_{max.}$ (cm.$^{-1}$)	Peak intensity (l. mole^{-1} cm.$^{-1}$)
Nitrobenzene	269·0	37,180	7,700
o-Dinitrobenzene	<210·0	>47,600	—
m- ,,	242·0	41,300	16,580
p- ,,	265·0	37,740	14,400
o-Nitrotoluene	265·0	37,740	5,500
m- ,,	274·0	36,500	7,300
p- ,,	283·5	35,260	9,220
2,3-Dinitrotoluene	<210·0	>47,600	—
2,4- ,,	252·0	39,700	14,100
2,5- ,,	266·5	37,510	11,600
2,6- ,,	241·0	41,500	8,980
3,4- ,,	219·0	45,690	10,040
3,5- ,,	248·0	40,300	12,020
1,2,4-Trinitrobenzene	235·0	42,530	15,440
1,3,5- ,,	227·0	44,070	12,500
2,3,4-Trinitrotoluene	238·5	41,190	12,340
2,3,5- ,,	238·5	41,190	17,440
2,3,6- ,,	258·0	38,760	8,960
2,4,5- ,,	237·0	42,190	14,040
2,4,6- ,,	232·0	43,100	18,620
3,4,5- ,,	242·0	41,300	16,720

Table 2.

Compound	Band frequencies (cm.$^{-1}$)		Integrated intensities per NO_2 group *		Band widths (cm.$^{-1}$)	
	ν_a	ν_s	$10^{-4}I_a$	$10^{-4}I_s$	$\Delta\nu_a$	$\Delta\nu_s$
Nitrobenzene	1534	1348	2·72	1·86	11·4	8·0
o-Nitrotoluene	1530	1349	2·85	1·90	13·8	15·4
m- ,,	1535	1350	2·71	1·89	11·9	8·1
p- ,,	1527	1346	2·45	2·25	10·9	7·1
o-Ethylnitrobenzene	1531	1352	2·59	2·13	16·5	19·3
p- ,,	1522	1348	2·53	2·28	20·0	10·0
o-Nitrobiphenyl	1534	1360	3·00	1·32	15·6	21·4
o-Nitroaniline	1516	1346	2·44	1·92	13·3	10·5
p- ,,	1509	1336	2·84	3·74	17·7	10·1
o-Nitrobenzaldehyde	1536	1348	2·90	1·95	16·6	12·7
p- ,,	1537	1347	2·64	1·86	17·5	13·9
o-Chloronitrobenzene	1540	1358	2·70	1·76	15·4	22·9
3-Nitro-4-t-butylaniline	—	1372	—	—	—	16·6
o-Nitro-t-butylbenzene	—	1375	—	—	—	16·3
o-Dinitrobenzene	1546	1368, 1350	3·59	1·71	17·6	18·0, 15·4
m- ,,	1542	1347	2·34	1·79	13·3	8·4
p- ,,	1542	1340	2·46	1·92	11·0	11·5
2,3-Dinitrotoluene	1552	1364, 1346	2·95	1·45	16·4	17·3, 13·1
2,4- ,,	1540	1348	2·10	1·80	15·0	12·1
2,5- ,,	1550	1346	2·76	1·64	18·0	12·6
2,6- ,,	1540	1363, 1348	2·68	1·78	17·8	26·8, 20·0
3,4- ,,	1548	1360, 1346	2·99	1·70	17·6	22·9, 13·1
3,5- ,,	1546	1356, 1341	2·18	1·68	12·9	12·6, 8·4
2,4-Dinitro-1-t-butylbenzene	1539	1372, 1352	3·18	2·37	25·3	16·3, 16·3
1,2,4-Trinitrobenzene	1562	1348	2·33	1·06	17·1	13·0
1,3,5- ,,	1557	1344	2·39	1·48	12·8	8·6
2,3,4-Trinitrotoluene	1572, 1558	1360, 1347	3·47	1·26	12·0, 28·4	16·3, 13·5
2,3,5- ,,	1563, 1549	1354, 1344	2·72	1·08	17·3, 12·3	10·3, 9·8
2,3,6- ,,	1573, 1557	1358, 1351	3·05	1·31	15·4, 14·8	22·4, 9·1
2,4,5- ,,	1566	1371, 1348	3·02	1·28	24·6	13·3, 18·4
2,4,6- ,,	1558	1354	2·70	1·36	16·4	14·0
3,4,5- ,,	1579, 1567	1369, 1350	2·90	1·26	16·0, 12·3	20·8, 15·6
2,4,6-Trinitrophenol	1554	1347	2·23	1·69	29·4	13·2

* Calculated from the total intensity of the doublet in the cases where splitting occurs.

spectra. Following Vandenbelt,[10] we considered only the most intense maxima, and these are assumed to correspond with his so-called " First Primary Band." Table 1 gives the wavelengths (mμ), frequencies (cm.$^{-1}$), and peak intensities of this band.

Infrared Spectra.—The frequencies (in wave-numbers) of the symmetric (ν_s) and asymmetric (ν_a) stretching modes of the nitro-group are collected in Table 2, cols. 2 and 3. Cols. 4 and 5 contain the mean value of the integrated intensity per nitro-group: these are calculated from the total intensity of the doublet in those cases where band-splitting occurs. The half-intensity band widths are shown in cols. 6 and 7 of Table 2.

Discussion

Ultraviolet Spectra.—Nitrobenzenes. In the following discussion the ultraviolet band shifts are considered relative to those of nitrobenzene, which is regarded as the parent compound of the whole series.

The spectra of the polynitrobenzenes can be interpreted by considering the polar interaction of several nitro-groups with the ring. The extensive conjugation of the nitro-group with the aromatic system lowers the electron density at certain ring positions so that additional nitro-substituents must compete for the available electron density with a reduction in the conjugation of each, and an increase in the energy of the excited state to give a hypsochromic displacement of the absorption band, as shown by the results for the di- and tri-nitrobenzenes. The selective withdrawal of electrons from certain ring positions suggests that the reduction in conjugation of several nitro-groups depends on their relative orientation, and accounts for the spectral differences between the *m*- and *p*-dinitrobenzenes.

In the case of *o*-dinitrobenzene steric hindrance must be considered. A pair of adjacent nitro-groups cannot both simultaneously occupy the coplanar configuration necessary for conjugation with the benzene ring. There are two possibilities: (*a*) one group is coplanar, with the second twisted out-of-plane; (*b*) both nitro-groups are twisted out-of-plane simultaneously. The spectral consequences of these alternatives are as follows. For (*a*), the spectrum should resemble that of the *meta*- or *para*-dinitro-compound. For (*b*), with neither group coplanar, the conjugation of both substituents with the ring is almost zero and the absorption should approach that of benzene itself. The fact that *o*-dinitrobenzene possesses no band above 210 mμ favours the second alternative, at least in the excited state. The introduction of a third nitro-group carries the decrease in conjugation a stage further and the two trinitrobenzenes examined absorb at somewhat shorter wavelengths than the *m*- and *p*-dinitro-compounds. The 1,2,4-isomer has a pair of vicinal nitro-groups which by analogy with *o*-dinitrobenzene should both be non-coplanar and therefore unconjugated. Their combined inductive effects will however still operate to reduce the conjugation of the group in the 4-position and produce the observed hypsochromic shift.

Nitrotoluenes. The results for *m*- and *p*-nitrotoluene are consistent with the $-I$ effect normally associated with the methyl group,[12] which tends to release electrons to the ring thereby enhancing conjugation of the nitro-group and resulting in the observed bathochromic displacements. In *o*-nitrotoluene this effect is more than neutralised by the steric effect which has been shown to occur between adjacent methyl and nitro-groups.[3,4] The steric effect is much less than that between vicinal nitro-groups and its influence on the spectrum is correspondingly smaller.

The discussion of the dinitrobenzenes and mononitrotoluenes suggests that the following factors are of importance in determining the ultraviolet characteristics of polynitroaromatic compounds: (*a*) A pair or more of nitro-groups tend partially to reduce their conjugation by mutual competition between their mesomeric-plus-inductive effect, and the magnitude of the reduction is determined by their relative positions around the ring. (*b*) A pair of vicinal nitro-groups interfere sterically with one another so that neither can be coplanar with the ring. (*c*) Methyl groups enhance the conjugation of nitro-groups

[12] Dewar, " The Electronic Theory of Organic Chemistry," Clarendon Press, Oxford, 1949, p. 52.

except when they are situated in the *ortho*-position: the latter circumstance introduces a small degree of steric hindrance.

The magnitude of these effects may be evaluated from the spectral data by considering the displacements ($\Delta\nu$) of the absorption maxima relative to nitrobenzene. These are given in Table 3. The significance of each $\Delta\nu$-value in terms of the factors (*a*), (*b*), and (*c*) described above is indicated in col. 4 by the appropriate symbol.

The six isomeric dinitrotoluenes may be regarded formally as composed of various combinations of the six disubstituted benzene derivatives. The factors (*a*), (*b*), and (*c*) being assumed to be additive, the values of $\Delta\nu$ in Table 3 enable the frequency shifts for the

TABLE 3.

Compound	ν (cm.$^{-1}$)	$\Delta\nu$ (cm.$^{-1}$)	Effect	Compound	ν (cm.$^{-1}$)	$\Delta\nu$ (cm.$^{-1}$)	Effect
Nitrobenzene	37,180	—	—	*o*-Nitrotoluene ...	37,740	560	(*c*)
o-Dinitrobenzene	>47,600	>10,420	(*a*), (*b*)	*m*- ,, ...	36,500	−680	(*c*)
m- ,,	41,300	4,120	(*a*)	*p*- ,, ...	35,260	−1,920	(*c*)
p- ,,	37,740	560	(*a*)				

dinitrotoluenes to be calculated. For example, 2,6-dinitrotoluene contains the following structural features: (i) one pair of *meta*-oriented nitro-groups, $\Delta\nu = 4120$ cm.$^{-1}$; (ii) a methyl group *ortho* to two nitro-groups, $\Delta\nu = 2 \times 560 = 1120$ cm.$^{-1}$; Total $\Delta\nu = 5240$ cm.$^{-1}$. Similar calculations were carried out for all six isomers. Adding to each value of $\Delta\nu$ the frequency for nitrobenzene (37,180 cm.$^{-1}$) gives a set of calculated frequencies which are compared with the observed values in Table 4.

TABLE 4. *Dinitrotoluenes.*

	2,3	2,4	2,5	2,6	3,4	3,5
ν (calc.)	>47,480	39,940	37,620	42,420	>45,000	39,940
ν (obs.)	>47,600	39,700	37,510	41,500	>45,690	40,300

The assumption of the additivity of the effects cannot be more than an approximation and with this in mind the agreement between the calculated and observed band positions is very satisfactory. The largest deviation occurs for the 2,6-isomer for which the calculated position is some 900 cm.$^{-1}$ too high. This suggests that the total steric effect between a methyl group and a nitro-group on each side of it is much less than twice the effect for a single nitro-group.

Owing to their increased complexity, the trinitrotoluenes cannot be analysed in this way and the small departures from additivity observed for the dinitrotoluenes are expected to be enhanced by a further substituent. Qualitatively the spectra follow patterns similar to those noted above. The introduction of a methyl group has the expected effect of increasing the conjugation of the nitro-groups through its $-I$ effect and the trinitrotoluenes all absorb at wavelengths somewhat longer than those of the corresponding trinitrobenzene. No 1,2,3-trinitrobenzene could be prepared to complete the series of comparisons.

The absorption bands of the trinitrotoluenes cover a smaller spectral range than those of the dinitro-series, indicating that the effect of extensive nitro-group substitution is to equalise the energies within a series of isomers. The mutual reduction of conjugation is a useful concept for the interpretation of the spectra of this class of compound. The effect approaches a limit when three nitro-groups are present since the mean frequencies for the mono-, di-, and tri-nitro-compounds are 36,670, 41,760, and 41,970 cm.$^{-1}$, respectively.

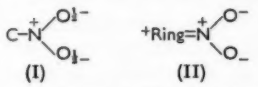
Infrared Spectra.—Band frequencies. The frequencies of the symmetric vibration of the nitro-group (Table 2, col. 3) exhibit little regularity with respect to the number and position of the nitro-substituents, probably owing to the interaction with the C–N vibration.[4,6] However, an empirical relation seems to exist between the incidence of steric effects and the shape of the band. In all compounds in which at least one nitro-group is strongly hindered the band splits into a doublet as shown in Table 2. In nearly

all other cases the band is single. The reason for this is not clear as the asymmetric band does not behave in this way, but the effect may nevertheless find useful practical application in structural diagnosis.

The asymmetric frequencies (Table 2, col. 2) confirm the observations of other workers [5,6] that powerful electron-donor groups such as NH_2 lower the frequency of this band in the mononitro-series from around 1534 cm.$^{-1}$ towards 1500 cm.$^{-1}$. The important result emerges that the frequencies as a whole fall into three ranges corresponding to the mono-, di-, and trinitro-series: Mononitro: $\nu_a = 1509$—1540, *i.e.*, <1540 cm.$^{-1}$; dinitro: $\nu_a = 1539$—1552 cm.$^{-1}$; trinitro: $\nu_a = 1554$—1567 cm.$^{-1}$. In some of the trinitro-compounds band splitting occurs but the range quoted is based on the lower-frequency component. Slight overlapping of the ranges occurs for the mono- and di-nitro-series, but in general the ranges are sufficiently distinct to be used as an indication of the degree of nitration of unknown compounds. The only serious discrepancies in the above correlations arise when a dinitro-compound also contains strong electron-donor groups such as NR_2; for example, *N*-methyl-2,4-dinitroaniline has $\nu_a = 1534$ cm.$^{-1}$, but this probably represents the maximum displacement of the dinitro-frequency into the mononitro-range.

The increased asymmetric frequency of the polynitro-compounds implies a high N–O bond order, and is consistent with the reduced conjugation of the nitro-groups in such compounds deduced from the ultraviolet spectra. With one exception (2,3,5-trinitrotoluene) the asymmetric band splits when three vicinal nitro-groups are present or when four substituents are in adjacent ring positions.

Integrated band intensities. The integrated band intensities per nitro-group (I_a and I_s) for the two stretching vibrations are shown in Table 2, cols. 4 and 5. The symmetrical band intensities show little regularity with the positions of the nitro-substituents although the values tend to fall as the number of nitro-groups increases. This is consistent with the ultraviolet data which indicate that several nitro-groups together are less fully conjugated than a single one. Structures (I) and (II) represent the charge distributions for the extreme cases of zero and full conjugation respectively. Reduced conjugation with the ring as in (I) should therefore lower the charge gradient and with it the band intensity, as observed.



(I) (II)

Clearly, a number of factors will influence the band intensities in these compounds. The asymmetric intensities might also be expected to follow a similar trend but this is not observed. It is of interest however that the highest values occur for those compounds which contain two or three vicinal nitro-groups: for the five compounds of this class which were studied, I_a lies above $2{\cdot}9 \times 10^4$.

Half-intensity band widths. The asymmetric band widths (Table 2, col. 6) show no correlation with the structural features, but the symmetric band widths reveal an interesting relation. The band width of an isolated nitro-group is in the range 8—11 cm.$^{-1}$, but the presence of small hindering groups (Me, Et) progressively broadens the band to 19 cm.$^{-1}$, without changing the frequency. This effect may be related to that observed by Orr [13] in the case of the C–H deformation bands in sterically hindered *trans*-stilbenes. Large blocking groups (Bu^t), however, lead to intermediate band widths of about 16 cm.$^{-1}$ with an accompanying rise in frequency towards 1375 cm.$^{-1}$, both of which values are close to those of the unconjugated nitro-group in nitromethane.

Thanks are offered to Dr. L. J. Bellamy for valuable discussions.

MINISTRY OF SUPPLY,
EXPLOSIVES RESEARCH AND DEVELOPMENT ESTABLISHMENT,
WALTHAM ABBEY, ESSEX. [*Received, May 25th*, 1959.]

[13] Orr, *Spectrochim. Acta*, 1956, **8**, 218.

666. *Organic Fluorine Compounds. Part XI.* Ethyl Fluoroacetoacetates and Fluoropyrimidines.*

By Ernst D. Bergmann, S. Cohen, and I. Shahak.

Ethyl bromo(or chloro)acetate condenses with ethyl fluoroacetate, and ethyl chlorofluoroacetate with ethyl acetate, in Reformatzky-type reactions to give ethyl γ- and α-fluoroacetoacetate, respectively. The enol from ethyl fluoroacetate condensed with acetyl chloride, benzoyl chloride, ethyl trifluoroacetate, and ethyl pentafluoropropionate to give the β-keto-esters. Fluoroacetone and acetic anhydride under catalysis by boron trifluoride give a β-diketone, probably 3-fluoropentane-2,4-dione.

By condensation of the available β-diketo-compounds with *S*-ethylisothiouronium bromide or urea, acetamidine, and guanidine several fluorine-containing pyrimidines have been prepared. Their ultraviolet and infrared spectra are discussed.

The purpose of the present study was to prepare fluoropyrimidines, which we expected to be antagonists of the corresponding hydrogen compounds. This expectation, which was based on the powerful antimetabolite properties of, *e.g.*, fluorophenylalanines and 5-fluorotryptophan, has meanwhile been borne out [1] to some extent for 5-fluorouracil, 5-fluoro-orotic acid, and 5-fluoroadenine.

First, fluorinated β-dicarbonyl compounds had to be made available. Several [2] are known, but their preparation is not always easy. Ethyl γ-fluoroacetoacetate, for example, has been prepared by Szinai [2] from fluoroacetyl chloride and ethyl dihydropyranyl malonate, and from ethyl t-butyl malonate (Fraser *et al.*[2]), but both methods are cumbersome, and the product requires lengthy purification.[3] It has now been found that ethyl γ-fluoroacetoacetate is easily accessible by reaction between ethyl bromoacetate (or better chloroacetate), ethyl fluoroacetate, and activated magnesium, though in ⩾40% yield. The reaction has been extended to the preparation of ethyl α-methyl- and (not quite pure) α-ethyl-γ-fluoroacetoacetate from ethyl α-bromo-propionate and -butyrate, respectively. The analogous reaction between ethyl bromofluoroacetate (which has already been used for Reformatzky reactions with aldehydes and ketones [4]), zinc, and ethyl acetate to give ethyl α-fluoroacetoacetate was made impracticable by the difficulty of preparing the brominated ester and its instability.[5] However, the analogous ethyl chlorofluoroacetate, which is accessible both by chlorination of ethyl fluoroacetate [6] and by hydrolysis of the ethanol adduct of chlorotrifluoroethylene,[7] gives the same Reformatzky-type reaction as the bromo-analogue.[8] Thus, ethyl α-fluoroacetoacetate was obtained from ethyl chlorofluoroacetate, an excess of ethyl acetate, and activated magnesium in 20% yield. As a by-product, ethyl γ-chloro-αγ-difluoroacetoacetate was formed. The latter was the principal product, when ethereal ethyl chlorofluoroacetate was refluxed with activated magnesium. Acceptable yields of ethyl α-fluoroacetoacetate can also be obtained by the reaction between the enol of ethyl fluoroacetate (prepared with sodium

* Part X, 1959, 1418.

[1] Duschinsky, Pleven, and Heidelberger, *J. Amer. Chem. Soc.*, 1957, **79**, 4559; Heidelberger and Duschinsky, U.S.P. 2,802,005; Heidelberger, Chaudhuri, Danneberg, Mooren, Griesbach, Duschinsky, Schnitzer, Pleven, and Scheiner, *Nature*, 1957, **179**, 6653; Montgomery and Hewson, *J. Amer. Chem. Soc.*, 1957, **79**, 4559.

[2] McBee, Pierce, Kilbourne, and Wilson, *J. Amer. Chem. Soc.*, 1953, **75**, 3152; Szinai, Thesis, Jerusalem, 1955; Fraser and Pattison, *Nature*, 1955, **176**, 696; Desirant, *Bull. Sci. Acad. roy. belges*, 1928, **15**, 966; Henne, Newman, Quill, and Staniforth, *J. Amer. Chem. Soc.*, 1947, **69**, 1819.

[3] Fraser, Millington, and Pattison, *J. Amer. Chem. Soc.*, 1957, **79**, 1959.

[4] McBee, Pierce, and Christman, *ibid.*, 1955, **77**, 1581.

[5] Haszeldine, *J.*, 1952, 4259; Swarts, *Rec. Trav. chim.*, 1898, **17**, 238; cf. Szinai.[6]

[6] Bergmann, Moses, Neeman, Cohen, Kaluszyner, and Reuter, *J. Amer. Chem. Soc.*, 1957, **79**, 4174.

[7] Young and Tarrant, *ibid.*, 1948, **71**, 2432; Englund, *Org. Synth.*, 1954, **34**, 49.

[8] Cf. Shriner, *Organic Reactions*, 1942, Vol. 1, p. 1.

hydride [9]) and acetyl chloride or acetic anhydride. Analogously, benzoyl chloride afforded ethyl α-benzoyl-α-fluoroacetate which is usually accompanied by some ethyl αα-dibenzoyl α-fluoroacetate. Reactions of the sodio-enolate of sodium acetate have been described recently.[10] Incidentally, it was found that the enol of ethyl fluoroacetate can be prepared even more easily from the ester with sodium ethoxide in low-boiling light petroleum.

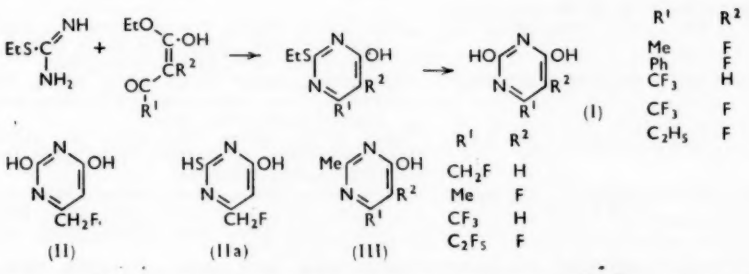
More highly fluorinated derivatives of ethyl acetoacetate can be obtained easily by reaction, catalyzed by sodium hydride, between ethyl fluoroacetate and ethyl trifluoroacetate or ethyl pentafluoropropionate.

Condensation of fluoroacetone and acetic anhydride in the presence of boron trifluoride gave an impure β-diketone, characterized as its copper chelate derivative. This is probably 3-fluoropentane-2 : 4-dione, the methylene group being favoured in such acylations,[11] but the position of the fluorine atom has not been rigidly established. An attempt to fluorinate 3-chloropentane-2 : 4-dione with potassium fluoride in ethylene glycol [12] gave only fluoroacetone, and this in low yield.

Pyrimidine Derivatives.—For the preparation of the pyrimidine derivatives, the condensation of the β-diketo-compounds with *S*-ethylisothiouronium bromide, in the presence of a basic catalyst, and subsequent hydrolysis with hydrochloric (in some cases, hydrobromic) acid [13] proved the best method. Thus were prepared the five compounds (I).

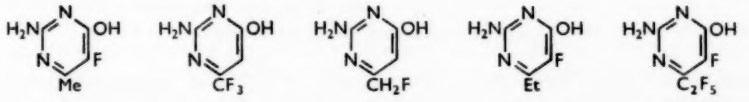
Ethyl γ-fluoroacetoacetate reacted with urea in the presence of hydrochloric acid [14] and gave 6-fluoromethyluracil (II), and with thiourea and sodium methoxide gave the mercaptopyrimidine (IIa), both in good yield.

Acetamidine was condensed easily by Snyder and Foster's method [15] with ethyl γ- and α-fluoro- and γγγ-trifluoro-acetoacetate and αγγδδδ-hexafluoro-β-oxovalerate to give the pyrimidines (III).



(II) (IIa) (III)

Finally, guanidine carbonate in boiling water [16] with ethyl α-fluoro- and γγγ-trifluoroacetoacetate gave compounds (IV) and (V), respectively. Also, guanidine condensed with



(IV) (V) (VI) (VII) (VIII)

ethyl γ-fluoroacetoacetate, α-fluoro-α-propionylacetate, and αγγδδδ-hexafluoro-β-oxovalerate in methanol, affording compounds (VI—VIII).

[9] Bergmann and Szinai, *J.*, 1956, 1521.
[10] DePree and Closson, *J. Amer. Chem. Soc.*, 1958, **80**, 2311.
[11] Hauser, Swamer, and Adams, *Organic Reactions*, 1954, Vol. 8, p. 98.
[12] Cf. Hoffmann, *J. Amer. Chem. Soc.*, 1948, **70**, 2596.
[13] Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 472; Johnson and Heyl, *ibid.*, 1907, **37**, 628.
[14] Cf. Donleavy and Kise, *Org. Synth.*, 1943, Coll. Vol. II, p. 422.
[15] Snyder and Foster, *J. Amer. Chem. Soc.*, 1954, **76**, 118.
[16] Wheeler and Johnson, *Amer. Chem. J.*, 1903, **29**, 496; Johnson and Clapp, *ibid.*, 1904, **32**, 130.

We have also condensed[17] urea and ethyl orthoformate with ethyl γ-fluoro- and γγγ-trifluoro-acetoacetate, obtaining the two α-ureidomethylene-compounds, but could not cyclize these products without some loss of fluorine.

Ultraviolet and infrared spectra of substituted 4-hydroxypyrimidines (in alcoholic solution and KBr *pellets, respectively).*

Substituents 2	5	6	$\lambda_{max.}$ (mμ) (log ε)	$\nu_{max.}$ (cm.$^{-1}$) *
OH	H	CH_2F	212 (3·90); 260 (3·92)	3200s, 3000s, 2890s, 1670s (CO), 1500m, 1430s, 1320m, 1245s, 1100, 1040 (C–F), 990, 900m, 795m, 765
OH	F	Me	268 (3·90)	3190s, 3050s, 2830s, 1667 (CO), 1500m, 1430s, 1320s, 1170, 1075s (C–F), 1020s (C–F), 885, 843s, 769m, 699m
OH	H	CF_3	262 (3·80)	3400, 3100s, 3000s, 2840s, 1730s and 1680s (CO), 1525m, 1440m, 1375s, 1280s (CF_3), 1215s (CF_3), 1170s (CF_3), 1110m, 995m, 900, 847m
OH	F	CF_3	223 (3·28); 272 (3·40); 310 (3·36)	3430, 3190s, 3050s, 2840s, 1680s (carbonyl), 1440, 1360s, 1290s (CF_3), 1182s (CF_3), 1045 (C–F), 925, 808m
OH	F	C_2F_5	212 (3·74); 272 (sh) (3·56)	3500, 3200m, 2850, 1680s (CO), 1430m, 1340m, 1285m, 1230m, 1170m, 1070m, 1030m, 990, 875, 800, 750
Me	H	CH_2F	224 (3·60); 273 (3·43)	3420, 3080s, 2860s, 2780s, 1680s (CO), 1620s, 1570m, 1448m, 1390m, 1350m, 1310, 1240, 1205m, 1080s (C–F), 995m, 955m, 920m, 886m, 860m, 765
Me	F	Me	226 (3·72); 270 (3·60)	3400, 3030, 2941, 2857m, 2778m, 1667s (CO), 1620s, 1450, 1389m, 1316m, 1205s, 1107, 1040 (C–F), 990, 952, 917m, 769m
Me	H	CF_3	219 (3·80); 280 (3·45)	2900s, 2800m, 1680s (CO), 1625m, 1600m, 1425m, 1320, 1290m, 1200s, 1120s, 1055, 1000, 963, 930, 895m, 772
Me	F	C_2F_5	221 (3·70); 280 (3·56)	3400, 3060m, 2950m, 2885m, 2880m, 1690s (CO), 1650m, 1388m, 1340m, 1316m, 1221s, 1175s, 1070m (C–F), 1030s (C–F), 935, 850, 781m, 735m, 690
Me	Me	CH_2F	220 (3·82); 272 (3·54)	
EtS	F	Me	237 (3·82); 290 (3·74)	3450, 2880m, 2810m, 2730m, 1660s (CO), 1610s, 1550s, 1460, 1410, 1380, 1360, 1270s, 1225s, 1170, 1130, 1090, 1065, 970m, 940m, 902m, 763m, 736m
EtS	F	CF_3	216 (3·90); 296 (3·61)	3400, 3080m, 3000m, 2900m, 2750m, 2650m, 1680s (CO), 1630m, 1560m, 1410s, 1270s, 1210s, 1190s, 1155s, 1063, 1010s, 970, 910, 875, 700m
EtS	F	C_2F_5	215 (4·01); 300 (3·54)	3500, 3000m, 2900m, 1680 (CO), 1610, 1550s, 1460, 1400m, 1340m, 1280s, 1220s, 1185s, 1160s, 1065s, 990s, 920, 838, 755, 725m, 690
EtS	F	Ph	208 (4·43); 250 (4·31); 306 (3·84)	3470, 3100m, 3000m, 2900m, 2800m, 2700m, 1670s (CO), 1600s, 1570s, 1500, 1450, 1420, 1385, 1320, 1270s, 1220, 1165, 1065, 1040, 1000m, 920m, 860, 760m, 740m, 690m, 680
NH_2	H	CF_3	223 (3·78); 295 (3·95)	3333s, 3200s, 2950, 1667s (CO), 1587s, 1495m, 1460s, 1360s, 1290s, 1205s, 1160s, 1040, 990s, 909, 833m, 800, 732m, 705m
NH_2	F	Me	220 (3·82); 292 (3·71)	3380s, 3140s, 3000s, 1667s (CO), 1630s, 1500s, 1450m, 1395m, 1370, 1260, 1240m, 1170, 1120, 1050, 1020m, 808m, 778m, 730, 665, 650m

* Bands not marked are of low strength.

Apart from certain fluorouracils (Duschinsky *et al.*[1]) and trifluoromethyl-,[18] fluorophenyl-, and fluorobenzyl-pyrimidines,[19] the compounds described here are the only known fluoro-derivatives of the pyrimidine series. [After completion of this study, two of the compounds prepared by us (I; $R^1 = CF_3$, $R^2 = H$) and (V) were described.[20]] Their toxicological and biochemical properties are being studied.

Spectra.—The ultraviolet spectra of pyrimidines have been studied by various authors;

[17] Whitehead, *J. Amer. Chem. Soc.*, 1952, **74**, 4267; 1953, **75**, 671.
[18] Miller, Dessert, and Anderson, *ibid.*, 1948, **70**, 500; Rutter and Gustafson, *J. Franklin Inst.*, 1954, **258**, 413.
[19] Curd and Rose, B.P. 581,347; Hitchings, Russell, and Falco, U.S.P. 2,594,309; Saijo, *J. Pharm. Soc. Japan*, 1952, **72**, 1444.
[20] Giner-Sorolla and Bendich, *J. Amer. Chem. Soc.*, 1958, **80**, 5744; see also Barone, Peters, and Tieckelmann, *J. Org. Chem.*, 1959, **24**, 198.

however, direct comparison with published data is difficult, because they have been determined in aqueous solutions of a given pH, whilst the present study is concerned with the neutral molecules (in alcohol). From the results summarized in the Table, we conclude that, whilst a 6-trifluoromethyl group has no appreciable effect on the spectrum of uracil, in which the chromophoric group is believed to be C:C·C:O, the addition of a 5-fluorine atom causes a significant bathochromic shift. The same is true for 4-hydroxy-2-methyl- and 2-ethylthio-4-hydroxy-pyrimidines.

Some infrared spectra of pyrimidine derivatives have also been reported.[21] Our observations (for the solid state) are summarized in the Table. In all compounds examined the carbonyl stretching frequency is very conspicuous, though Short and Thompson [21] did not find such a peak in the spectrum of 4-hydroxy-6-methyl-2-methylthiopyrimidine. The C–F band is well pronounced in the pyrimidines that contain trifluoromethyl and pentafluoroethyl groups; if the fluorine is attached to the 5-position, the band is either weak or appears to be shifted.

Experimental

Ethyl γ-Fluoroacetoacetate.—(*a*) To a stirred mixture of ethyl fluoroacetate (21 g.), magnesium turnings (7·2 g.), mercuric chloride (0·5 g.), and anhydrous ether (70 ml.), 10—20 ml. of a solution of ethyl bromoacetate (33 g.) in ether (50 ml.) were added and the mixture was heated until an exothermic reaction set in. The remainder of the bromoacetate solution was then added during 30—45 min., with cooling if necessary. The mixture was refluxed for 30 more min., cooled, and decomposed with ice and sulphuric acid. The ethereal layer was separated, and the aqueous layer extracted once with ether; the combined ethereal extracts were dried (Na_2SO_4) and distilled, giving ethyl γ-fluoroacetate (6 g., 20%), b. p. 87—88°/24 mm. (Found: C, 48·1; H, 5·8. Calc. for $C_6H_9O_3F$: C, 48·6; H, 6·1%).

(*b*) A mixture of magnesium (18 g.), mercury (about 10 g.), and anhydrous ether (30 ml.) was refluxed gently, with stirring, until a homogeneous grey suspension had been formed. A mixture (10—20 ml.) of ethyl fluoroacetate (80 g.), ethyl chloroacetate (62 g.), and ether (300 ml.) was added. Usually, an exothermic reaction set in at once; if not, heating was continued until reaction started. The balance of the solution was then added at such a rate that the mixture continued to boil, without external heating. The product was finally refluxed for 30 min., cooled, and decomposed with ice and sulphuric acid. After a head fraction of ethyl fluoroacetate (16—20 g.), the product (50 g.) boiled at 96—99°/30 mm.

Analogously, *ethyl γ-fluoro-α-methylacetoacetate* was obtained (4 g., 19%) from ethyl fluoroacetate (15 g.), magnesium (5 g.), mercuric chloride, and ethyl α-bromopropionate (25 g.). It had b. p. 90—93°/25 mm., $\nu_{max.}$ (liquid) 3500, 3000, 1730, and 1705s (doublet, C=O), 1460, 1370, 1100(br), 1050(br), 865, 810 $cm.^{-1}$ (Found: C, 51·8; H, 6·7. $C_7H_{11}O_3F$ requires C, 51·8; H, 6·8%).

Impure ethyl α-ethyl-γ-fluoroacetoacetate, obtained in 19% yield from ethyl fluoroacetate (21 g.), magnesium (7·2 g.), mercuric chloride, and ethyl α-bromobutyrate (37 g.), had b. p. 89—91°/22 mm. (Found: C, 52·3; H, 7·1. Calc. for $C_8H_{13}O_3F$: C, 54·5; H, 7·4%).

Ethyl α-Fluoroacetoacetate.—(*a*) To a stirred mixture of ethyl acetate (dried over P_2O_5) (54 g.), magnesium turnings (4·8 g.), mercuric chloride, and absolute ether (100 ml.), 10—15 ml. of a solution of ethyl chlorofluoroacetate (28 g.) in ether (50 ml.) were added, and heat was applied until reaction set in. The remainder of the chlorofluoroacetate solution was added dropwise in 30—45 min., then the mixture was refluxed for about 30 min., cooled, and worked up as described above. Distillation gave ethyl α-fluoroacetoacetate, b. p. 83—85°/19 mm. (6 g., 20%), and ethyl γ-chloro-αγ-difluoroacetoacetate, b. p. 103—104°/19 mm. (1·5 g., 8%).

(*b*) Ethyl fluoroacetate (36 g.) was added dropwise to a suspension of sodium hydride (8 g.) in anhydrous ether, under nitrogen, after the reaction had been initiated by addition of 0·5 ml. of anhydrous ethanol.[9] The suspension was stirred at room temperature for about 3 hr., during which most of the hydride reacted; anhydrous ether was added from time to time in order to keep the mixture fluid. Then acetyl chloride (26 g.) in ether (50 ml.) was added, with cooling, during 20 min. The mixture was stirred for 1 hr. at room temperature, then poured on ice and sulphuric acid, and the organic material was isolated as usual, giving ethyl α-fluoroacetoacetate

[21] Brownlie, *J.*, 1950, 3062; Short and Thompson, *J.*, 1952, 168; Brown and Short, *J.*, 1953, 331; Brown, Hoerger, and Mason, *J.*, 1955, 211.

(16·5 g., 34%), b. p. 83—85°/19 mm., n_D^{27} 1·4046 (decomposes on prolonged storage and gives off acid fumes), $\nu_{max.}$ (liquid) 3500, 3000s, 2950, 1750, and 1725vs (doublet, carbonyl), 1475, 1450, 1425, 1365vs, 1290—1260vs, 1120vs, 1020vs, 970, 940, 863, 765 cm.$^{-1}$.

A fraction (6 g.) of n_D^{24} 1·4210 and b. p. 93—94°/1 mm. was also isolated. It was thought to be ethyl αα-diacetyl-α-fluoroacetate in analogy with benzoylation of the enol of ethyl fluoroacetate; however, analysis showed that the product contained a substance richer in fluorine (Found: F, 14·6. Calc. for $C_8H_{11}O_4F$: F, 10·0%). It is assumed that some ethyl αγ-difluoroacetoacetate is formed which is further acetylated in the α-position to yield $CH_2F{\cdot}CO{\cdot}CFAc{\cdot}CO_2Et$ (calc.: F, 18·5%).

(*c*) To a suspension of sodium methoxide (1·8 g.) in light petroleum (b. p. 40—60°; 100 ml.), ethyl fluoroacetate (15·9 g.) was added slowly at 15—25° with shaking. Thus a homogeneous, microcrystalline suspension of the yellowish voluminous enolate was obtained. After 10 minutes' additional shaking, freshly distilled acetyl chloride (11·5 g.) was added, and the mixture shaken at room temperature for 1 hr., refluxed for 10 min., and treated with water. The organic layer was separated, washed with 1% sodium hydrogen carbonate solution, dried, and concentrated in a short column. The residue boiled at 87—90°/23 mm. (5 g., 15%). When instead of the acetyl chloride, acetic anhydride (15·7 g.) was used, a yield of 10% (3·5 g.) of ethyl α-fluoroacetoacetate was obtained (Found: C, 48·4; H, 5·9; F, 13·0. Calc. for $C_6H_9O_3F$: C, 48·6; H, 6·1; F, 12·8%).

Ethyl α-Fluoro-β-oxovalerate.—To the enolate, prepared from ethyl fluoroacetate (53 g.) and sodium hydride (12 g.), propionyl chloride (47 g.) was added dropwise. The solution was stirred and refluxed for 4 hr. Water was added with stirring and the ethereal layer separated, dried (Na_2SO_4) and distilled. Thus were obtained: (a) *ethyl α-fluoro-β-oxovalerate* (17 g., 21%), b. p. 105—107°/32 mm., n_D^{30} 1·4090, $\nu_{max.}$ (liquid film) 3000s, 1735vs, 1450, 1220—1280vs,br, 1136vs, 1105vs, 1020, 940, 855 cm.$^{-1}$ (Found: C, 50·5; H, 6·9. $C_7H_{11}O_3F$ requires C, 51·8; H, 6·8%); and (b) a fraction, b. p. 105—106°/3 mm. (10 g.), probably a mixture of ethyl αα-dibenzoyl-α-fluoroacetate and α-fluoro-α-fluoroacetyl-β-oxovalerate.

Ethyl γ-Chloro-αγ-difluoroacetoacetate.—A stirred mixture of ethyl chlorofluoroacetate (29 g.), magnesium turnings (2·4 g.), mercuric chloride (0·5 g.), and anhydrous ether (100 ml.) was refluxed gently until all the magnesium had disappeared. After one more hour at the b. p., the mixture was poured on ice and sulphuric acid, and the *ester* (10·5 g., 52%) isolated as usual; it had b. p. 101—104°/19 mm., $\nu_{max.}$ (liquid) 3400s, 2950, 1730s(CO), 1400, 1380, 1310, 1230, 1090—1100, 1050—1060, 880, 860, 790 cm.$^{-1}$ (Found: C, 35·8; H, 4·1. $C_6H_7O_3ClF_2$ requires C, 36·0; H, 3·5%).

Ethyl α-Benzoyl-α-fluoroacetate.—(*a*) To a suspension of the enol of ethyl fluoroacetate (53 g.), prepared with sodium hydride (12 g.) in anhydrous ether (200 ml.) as described above, benzoyl chloride (71 g.) was added with stirring and cooling in 30 min. Stirring at room temperature was continued for 2 hr., then the mixture was poured into ice-cold sulphuric acid, and the ethereal layer was separated, washed with water and dilute sodium carbonate solution, and dried (Na_2SO_4). The *ester* (32 g., 30%), on redistillation, had b. p. 125—128°/4 mm. (Found: C, 62·1; H, 5·0; F, 9·7. $C_{11}H_{11}O_3F$ requires C, 62·9; H, 5·2; F, 9·1%).

(*b*) To the enol of ethyl fluoroacetate, prepared as above from the ester (15·9 g.) and sodium methoxide (1·8 g.) in light petroleum (100 ml.), benzoyl chloride (21 g.) was added. The product was worked up as described for the analogous preparation of ethyl α-fluoroacetoacetate and isolated by distillation *in vacuo*, b. p. 125—130°/1 mm. (6 g., 20%) (Found: C, 63·2; H, 5·1%).

The 2 : 4-*dinitrophenylhydrazone*, which recrystallized from nitromethane, melted at 190° (Found: C, 52·3; H, 3·7; N, 14·2. $C_{17}H_{15}O_6N_4F$ requires C, 52·3; H, 3·8; N, 14·4%).

A second fraction (10 g., 22%) boiled at 165—170°/1 mm., and was identified by the analysis as *ethyl αα-dibenzoyl-α-fluoroacetate* (Found: C, 69·1; H, 4·7; F, 5·9. $C_{18}H_{15}O_4F$ requires C, 68·8; H, 4·8; F, 6·0%).

Ethyl γγγ-Trifluoro- and αγγγ-Tetrafluoro-acetoacetate.—These were prepared as described by McBee *et al.*[3] The infrared spectrum of the second ester was measured (liquid film): 3500, 3050, 1770, 1695, 1460, 1390, 1130 (all vs), 925, 862, 790, 680 cm.$^{-1}$.

Ethyl αγγδδδ-Hexafluoro-β-oxovalerate.—Ethyl fluoroacetate (21 g.) was added with stirring to a boiling mixture of ethyl pentafluoropropionate (38 g.), sodium hydride (5 g.), and anhydrous ether (100 ml.) in 3 hr. Stirring and heating were continued for a further 4 hr., then the mixture was decomposed with sulphuric acid and ice and extracted with ether, and the extract distilled

under reduced pressure. The *ester* (35 g., 70%), on redistillation from phosphorus pentoxide, had b. p. 63—64°/27 mm., n_D^{27} 1·3394, $\nu_{max.}$ (liquid) 3450, 3000, 1750sh, 1720, 1170vbr, 860 cm.$^{-1}$ (Found: C, 33·4; H, 2·8. $C_7H_9O_3F_5$ requires C, 33·3; H, 2·4%).

6-Fluoromethyluracil (II).—A mixture of finely powdered urea (8·5 g.), ethyl γ-fluoroacetoacetate (19·5 g.), anhydrous ethanol (5 c.c.), and concentrated hydrochloric acid (2—3 drops) in a loosely covered porcelain dish was placed in an evacuated desiccator for 5—6 days; from time to time the mass was broken up. The resulting solid, finely powdered, was added to a solution of sodium hydroxide (8 g.) in water (120 ml.) at 90—95°. When all the solid had dissolved, the solution was cooled rapidly and excess of hydrochloric acid added, whereupon *6-fluoromethyluracil* crystallized (12 g., 73%); it had m. p. 270—272° (from acetic acid) (Found: C, 41·8; H, 4·0; F, 13·6. $C_5H_5O_2N_2F$ requires C, 41·7; H, 3·5; F, 13·2%).

6-Fluoromethyl-4-hydroxy-2-mercaptopyrimidine (IIa).—Ethyl γ-fluoroacetoacetate (9 g.), thiourea (4·6 g.) and 2M-methanolic sodium methoxide (30 ml.) were kept together for 48 hr. at room temperature. The solvent was removed under reduced pressure, the residue dissolved in water, and the solution acidified with acetic acid and left overnight. The *pyrimidine* (6·5 g., 67%) that had crystallized was filtered off and washed with water. After recrystallization from acetic acid, it melted at 232—236° (decomp.) (Found: F, 12·0. $C_5H_5ON_2FS$ requires F, 11·9%).

Reactions with S-Ethylisothiouroninm Bromide.—2-Ethylthio-5-fluoro-4-hydroxy-6-methylpyrimidine. A mixture of ethyl α-fluoroacetoacetate (19 g.), *S*-ethylisothiouronium bromide (24 g.), and 2M-methanolic sodium methoxide (64 ml.) was refluxed for 12 hr. The solvent was removed under reduced pressure and the residue taken up in water and acidified with hydrochloric acid. A little ether was added and the mixture stirred vigorously to induce crystallization. The *product* (11 g., 46%) had m. p. 190—192° (from ethyl acetate) (Found: C, 44·4; H, 4·8. $C_7H_9ON_2FS$ requires C, 44·7; H, 4·8%).

2-Ethylthio-5-fluoro-4-hydroxy-6-phenylpyrimidine. A mixture of ethyl α-benzoyl-α-fluoroacetate (19 g.), *S*-ethylisothiouronium bromide (19 g.), and 2M-sodium methoxide (50 ml.) was refluxed for 6 hr. The *pyrimidine* (4·5 g., 20%) had m. p. 235—240° (from ethyl acetate) (Found: C, 57·3; H, 4·7. $C_{12}H_{11}ON_2FS$ requires C, 57·6; H, 4·4%).

2-Ethylthio-4-hydroxy-6-trifluoromethylpyrimidine. The crude *product* from ethyl γγγ-trifluoroacetoacetate (32 g.), *S*-ethylisothiouronium bromide (32 g.) and 2M-sodium methoxide (70 ml.) was dissolved in a little ethyl acetate and precipitated by excess of ether. It (17 g., 45%) had m. p. 176—178° (Found: C, 37·6; H, 3·4. $C_7H_7ON_2F_3S$ requires C, 37·5; H, 3·1%).

2-Ethylthio-5-fluoro-4-hydroxy-6-trifluoromethylpyrimidine. The crude *product* (11 g., 25%) formed from ethyl αγγγ-tetrafluoroacetoacetate (37 g.), *S*-ethylisothiouronium bromide (34 g.) and 2M-sodium methoxide (92 ml.) and recrystallized from aqueous acetic acid and then from light petroleum (b. p. 60—70°) had m. p. 136—138° (Found: C, 35·3; H, 2·6. $C_7H_6ON_2F_4S$ requires C, 34·2; H, 2·5%).

2-Ethylthio-5-fluoro-4-hydroxy-6-pentafluoroethylpyrimidine. Ethyl αγγδδδ-hexafluoro-β-oxovalerate (25 g.), *S*-ethylisothiouronium bromide (18·5 g.) and a solution of sodium (4 g.) in methanol (50 ml.) gave a *product* which after recrystallization from aqueous acetic acid melted at 159—160° (10 g., 35%) (Found: F, 38·4; N, 9·0. $C_8H_6ON_2F_6S$ requires F, 39·0; N, 9·6%).

5-Fluoro-2,4-dihydroxy-6-methylpyrimidine (I; R^1 = Me, R^2 = F).—2-Ethylthio-5-fluoro-4-hydroxy-6-methylpyrimidine (3 g.) was refluxed for 3 hr. with acetic acid (15 ml.) and concentrated hydrochloric acid (4 ml.). Upon cooling, 1 g. (44%) of the *dihydroxypyrimidine* was obtained; it recrystallized from acetic acid and decomposed above 300° (Found: C, 41·9; H, 3·6; F, 13·0. $C_5H_5O_2N_2F$ requires C, 41·7; H, 3·5; F, 13·2%).

5-Fluoro-2,4-dihydroxy-6-phenylpyrimidine (I; R^1 = Ph, R^2 = F) was obtained from 2-ethylthio-5-fluoro-4-hydroxy-6-phenylpyrimidine (3 g.) with refluxing acetic acid (15 ml.) and 40% hydrobromic acid (15 ml.) for 3 hr. On cooling, 1 g. (41%) of material was obtained, having m. p. 290—295° (from acetic acid) (Found: C, 58·1; H, 3·5; F, 10·1. $C_{10}H_7O_2N_2F$ requires C, 58·3; H, 3·4; F, 9·2%).

2,4-Dihydroxy-6-trifluoromethylpyrimidine (I; R^1 = CF_3, R^2 = H) was obtained by refluxing 2-ethylthio-4-hydroxy-6-trifluoromethylpyrimidine (17 g.) with acetic acid (60 ml.) and concentrated hydrochloric acid (40 ml.) for 8 hr. On cooling, 10 g. (73%) of the pyrimidine, m. p. 225—227° (from ethyl acetate), was obtained (Found: C, 33·4; H, 2·0; F, 30·5. $C_5H_3O_2N_2F_3$ requires C, 33·3; H, 1·7; F, 31·3%).

5-Fluoro-2,4-dihydroxy-6-trifluoromethylpyrimidine (I; R^1 = CF_3, R^2 = F) was prepared

by refluxing for 24 hr. 2-ethylthio-5-fluoro-4-hydroxy-6-trifluoromethylpyrimidine (10 g.) with acetic acid (25 ml.) and 40% hydrobromic acid (50 ml.). The solution was brought to dryness under reduced pressure, and the residue refluxed with carbon tetrachloride (100 ml.) for 5—6 hr. which removed impurities without dissolving the product. The latter was filtered off and recrystallized from ethyl acetate [4 g., 47%; m. p. 224—227° (from ethyl acetate)] (Found: C, 30·5; H, 0·7; F, 38·3. $C_5H_2O_2N_2F_4$ requires C, 30·3; H, 1·0; F, 38·4%).

5-Fluoro-2,4-dihydroxy-6-pentafluoroethylpyrimidine (I; $R^1 = C_2F_5$, $R^2 = F$).—When 2-ethylthio-5-fluoro-4-hydroxy-6-pentafluoroethylpyrimidine (8 g.) was refluxed for 30 hr. with acetic acid (20 ml.) and 40% hydrobromic acid (40 ml.), the product crystallized on cooling. Recrystallized from aqueous acetic acid, it (5 g., 68%), had m. p. 221—222°. In spite of the sharp m. p., no satisfactory analysis could be obtained (Found: C, 30·3; H, 1·3. Calc. for $C_6H_2O_2N_2F_6$: C, 29·0; H, 0·8%).

4-Fluoromethyl-6-hydroxy-2-methylpyrimidine (III; $R^1 = CH_2F$, $R^2 = H$).—A mixture of acetamidine hydrochloride [22] (6·5 g.), ethyl γ-fluoroacetoacetate (10 g.), and 2M-sodium methoxide (34 ml.) was kept over sulphuric acid under reduced pressure, until a dry residue was left. This was extracted with hot ethanol, and the *product* (2 g., 21%) precipitated by ether. After recrystallization from ethanol, it melted at 204—207° (Found: C, 50·9; H, 4·8. $C_6H_7ON_2F$ requires C, 50·7; H, 4·9%).

5-Fluoro-4-hydroxy-2,6-dimethylpyrimidine (III; $R^1 = Me$, $R^2 = F$).—Ethyl α-fluoroacetoacetate (15 g.) was added to a solution of acetamidine hydrochloride (9·5 g.) in 2M-methanolic sodium methoxide (100 ml.), whereupon an exothermic reaction took place. The mixture was left overnight, the solvent was removed under reduced pressure, and the residue taken up with a little water, acidified with acetic acid, and brought to dryness under reduced pressure. From boiling ethanol, 8 g. (56%) of the *product*, m. p. 177—178°, were obtained (Found: C, 50·9; H, 5·3%).

4-Hydroxy-2-methyl-6-trifluoromethylpyridimine (III; $R^1 = CF_3$, $R^2 = H$).—To a mixture of acetamidine hydrochloride (9·5 g.) and ethyl γγγ-trifluoroacetoacetate (18·4 g.), powdered sodium hydroxide (4 g.) was added in small portions, with stirring; an exothermic reaction took place. The mixture was kept under reduced pressure over sulphuric acid till dry, powdered, mixed with sodium hydrogen carbonate, and extracted with ethyl acetate (Soxhlet). On evaporation of the solvent under reduced pressure, a *product* (14 g., 73%) was obtained, which was washed with water and recrystallized from toluene, then having m. p. 134—136° (Found: C, 40·9; H, 3·0. $C_6H_5ON_2F_3$ requires C, 40·5; H, 2·8%).

5-Fluoro-4-hydroxy-2-methyl-6-pentafluoroethylpyrimidine (III; $R^1 = C_2F_5$, $R^2 = F$).—Ethyl αγγδδδ-hexafluoro-β-oxovalerate (4·5 g.) was added to a solution of acetamidine hydrochloride (1·9 g.) in 2M-methanolic sodium methoxide (20 ml.). The mixture was kept overnight, the solvent removed under reduced pressure, the residue dissolved in a little water, and the solution acidified with hydrochloric acid. The *product* (2 g., 43%), recrystallized from aqueous ethanol, melted at 105—106° (Found: C, 34·3; H, 1·6. $C_7H_4ON_2F_6$ requires C, 34·1; H, 1·6%).

2-Amino-5-fluoro-4-hydroxy-6-methylpyrimidine (IV).—Ethyl α-fluoroacetoacetate (15 g.) was added to a solution of guanidine carbonate (18 g.) and potassium hydroxide (6 g.) in water (50 ml.) and refluxed for 3 hr., cooled, and acidified carefully with acetic acid. The resulting precipitate was digested with boiling acetic acid, filtered, and recrystallized from dimethylformamide. The *pyrimidine* was a buff-coloured powder (8 g., 46%), decomp. >300° (Found: C, 42·5; H, 4·8; F, 13·7. $C_5H_6ON_3F$ requires C, 42·0; H, 4·2; F, 13·3%).

2-Amino-4-hydroxy-6-trifluoromethylpyrimidine (V).—Ethyl γγγ-trifluoroacetoacetate (4 g.), guanidine carbonate (4 g.), and a solution of sodium hydroxide (2 g.) in water (10 ml.) were refluxed for 2 hr. On cooling and neutralization with acetic acid, the *product* (13 g., 26%) was precipitated. It recrystallized from acetic acid and liquefied in the neighbourhood of 170° (but sublimation is too rapid to permit accurate determination of the m. p.) (Found: C, 33·8; H, 2·1. $C_5H_4ON_3F_3$ requires C, 33·5; H, 2·2%).

2-Amino-4-fluoromethyl-6-hydroxypyrimidine (VI).—Ethyl γ-fluoroacetoacetate (14·8 g.) and guanidine hydrochloride (9·6 g.) in 2M-sodium methoxide (100 ml.) were kept at room temperature for 48 hr. with occasional shaking. The solvent was removed under reduced pressure, and the solid residue dissolved in water, filtered, and acidified with acetic acid, whereupon the *pyrimidine* crystallized in quantitative yield (14 g.). Recrystallized from hot glacial acetic acid, it had m. p. 250—260° (decomp.) (Found: F, 12·9. $C_5H_6ON_3F$ requires F, 13·2%).

[22] Dox, *Org. Synth.*, 1942, Coll. Vol. I, p. 5.

2-Amino-4-ethyl-5-fluoro-6-hydroxypyrimidine (VII).—This compound was prepared by the same procedure from ethyl α-fluoro-α-propionylacetate (6·5 g.), guanidine hydrochloride (4 g.), and methanolic 2M-sodium methoxide (40 ml.). The *pyrimidine* (3 g., 48%) crystallized from the acidified aqueous solution in 48 hr. The analytical sample was prepared by sublimation at 220°/1 mm. (Found: C, 45·3; H, 5·4; F, 12·2. $C_6H_8ON_3F$ requires C, 45·9; H, 5·1; F, 12·1%).

2-Amino-5-fluoro-4-hydroxy-6-pentafluoroethylpyrimidine (VIII).—Ethyl α-fluoro-α-pentafluoropropionylacetate (17 g.) and guanidine hydrochloride (6·7 g.) in 2M-methanolic sodium methoxide (67 ml.) were kept at room temperature for 48 hr. with occasional shaking. After removal of the solvent under reduced pressure, the residue was taken up in water and acidified with excess of acetic acid; the solution was brought to dryness and the residue shaken with ether to induce crystallization. The *product* was filtered off (8 g., 49%) and purified by sublimation *in vacuo*. It then melted at 265—268° (Found: C, 29·6; H, 1·0; F, 45·9. $C_6H_3ON_3F_6$ requires C, 29·2; H, 1·2; F, 46·1%).

Ethyl γ-Fluoro-α-ureidomethyleneacetoacetate.—A mixture of urea (3 g.), ethyl orthoformate (8 g.), and ethyl γ-fluoroacetoacetate (7·5 g.) was refluxed for 6 hr., cooled and diluted with excess of ether. The crude *product* (4·8 g., 36%) which was precipitated was purified by washing with water and recrystallization from hot ethanol; it decomposed above 200° (Found: C, 44·6; H, 5·3; F, 9·0. $C_8H_{11}O_4N_2F$ requires C, 44·0; H, 5·1; F, 8·7%).

Cyclization with refluxing sodium methoxide solution [17] gave only a brown ill-defined product.

Ethyl γγγ-Trifluoro-α-ureidomethyleneacetoacetate.—A mixture of urea (4·5 g.), ethyl orthoformate (12 g.), and ethyl γγγ-trifluoroacetoacetate (14 g.) was refluxed for 6 hr., cooled, and diluted with much ether. The *product* (10 g., 52%), recrystallized from ethanol, melted at 170—172° (Found: C, 37·8; H, 3·6. $C_8H_9O_4N_2F_3$ requires C, 37·8; H, 3·6%). After the product (5 g.) had been refluxed for 30 min. with sodium hydroxide (1 g.) in water (10 c.c.), acidification with hydrochloric acid gave a compound (2 g.), m. p. 261—265° (from acetic acid), which contained 6% less fluorine than the expected 2-hydroxy-6-trifluoromethylpyrimidine-4-carboxylic acid.

Acylation of Fluoroacetone with Acetic Anhydride.—A mixture of fluoroacetone [23] (38 g.) and acetic anhydride (130 g.) was saturated with boron trifluoride at $+10°$. Then, water (750 ml.) and anhydrous sodium acetate (150 g.) were added and the mixture was distilled. Most of the diketone was found in the first 500 ml. of distillate. To this portion, a filtered solution of copper acetate (60 g.) in hot water (200 ml.) was added, and the light blue chelate salt filtered off after 12 hr. and washed with water. It was taken up with a solution of sulphuric acid (40 ml.) in water (200 ml.) and extracted repeatedly with ether. The ethereal extract was dried (Na_2SO_4) and distilled, to yield 26 g. (49%) of fluoroacetylacetone, b. p. 49—51°/30 mm. As the compound decomposed on storage, no satisfactory analysis could be obtained. Attempts to condense it with urea by using sulphuric acid,[24] or with guanidine carbonate by using fuming sulphuric acid, failed.

3-Chloropentane-2,4-dione and Potassium Fluoride.—When the dione [26] (180 g.) was added dropwise to a stirred mixture of potassium fluoride (116 g.) and ethylene glycol (200 g.) at 180° and the fluorinated material allowed to distil off continuously, only impure fluoroacetone (25 g.) was obtained.

This work was sponsored by the United States National Institute of Health.

Department of Organic Chemistry,
Hebrew University, Jerusalem.
Scientific Department, Ministry of Defence,
Tel-Aviv, Israel.

[*Received, January 23rd*, 1959.]

[23] Bergmann and Cohen, *J.*, 1958, 2259.
[24] Hale, *J. Amer. Chem. Soc.*, 1914, **36**, 104.
[25] Roblin, Winnek, and English, *ibid.*, 1942, **64**, 567.
[26] von Auwers and Auffenberg, *Ber.*, 1917, **50**, 929.

XUM

667. *Organic Fluorine Compounds. Part XII.* Preparation and Reactions of Diethyl Fluoromalonate.*

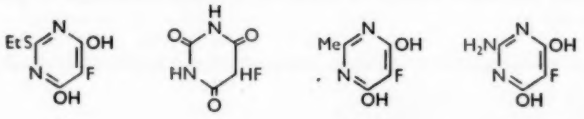
By Ernst D. Bergmann, Sasson Cohen, and Israel Shahak.

The exchange reaction of diethyl bromomalonate with potassium fluoride gives only diethyl difluoromalonate, but diethyl fluoromalonate has been prepared by pyrolysis of diethyl oxalofluoroacetate and by reaction of diethyl sodio-fluoroacetate with ethyl chloroformate. Some reactions of diethyl fluoromalonate have been investigated.

The variety of syntheses possible with diethyl malonate and the biochemical properties of malonic acid made fluoromalonic acid an attractive compound. LaZerte and his co-workers [1] have described an 8-stage synthesis of this acid from trifluorochloroethylene, but a more convenient route appeared to be by reaction of diethyl bromomalonate with potassium fluoride at 180—190°.[2] When this reaction was repeated or carried out in acetamide as solvent,[3] a fairly constant-boiling product was obtained which had the expected carbon and hydrogen content, but contained only half the expected amount of the fluorine; it was a mixture of 3 parts of diethyl malonate and 1 part of diethyl difluoromalonate. The latter was obtained pure by brominating the mixture and separating diethyl difluoromalonate by distillation from the bromination products of the malonate. Also the amides prepared from the mixture could be separated by fractional recrystallisation from water. Difluoromalondiamide had the melting point indicated in the literature [4] for a product obtained by a different route. It seemed possible that the monofluoromalonate first formed might undergo the reaction, $CHF(CO_2Et)_2 + CHBr(CO_2Et)_2 \longrightarrow CH_2(CO_2Et)_2 + CFBr(CO_2Et)_2$, the bromofluoro-ester then undergoing further halogen exchange, but this should lead to a 1 : 1 mixture, so the reaction is clearly more complex.

Diethyl monofluoromalonate was obtained by (*a*) pyrolysis of diethyl oxalofluoroacetate at 210—220° (34% yield), analogously to the formation of diethyl methylmalonate from diethyl oxalopropionate,[5] and (*b*) by reaction of ethyl sodiofluoroacetate, which is fairly stable,[6] with ethyl chloroformate (20—25% yield). A higher-boiling fraction $C_9H_{12}O_5F_2$, obtained in the latter reaction, was diethyl α-fluoro-α-fluoroacetylmalonate, $CH_2F{\cdot}CO{\cdot}CF(CO_2Et)_2$. Hydrolysis and ammonolysis were accompanied by "acid fission" and led to fluoromalonic acid and fluoromalondiamide, respectively. It is assumed that part of the enol of ethyl fluoroacetate is converted into the enol of ethyl αγ-difluoroacetoacetate and only then reacts with ethyl chloroformate (see preceding paper).

In an attempt to prepare 5-fluorobarbituric acid (II), diethyl fluoromalonate was condensed with *S*-ethylisothiouronium bromide in the presence of sodium methoxide.



(I) (II) (III) (IV)

The 2-ethylthio-5-fluoro-4,6-dihydroxypyrimidine (I) obtained gave, with the usual reagents (aqueous hydrochloric, hydrobromic, or chloroacetic acid) only a water-soluble

* Part XI, preceding paper.

[1] LaZerte, Rausch, Koshar, Park, Pearlson, and Lacher, *J. Amer. Chem. Soc.*, 1956, **78**, 5639.
[2] Gryszkiewicz-Trochimowski, Sporzynski, and Wnuk, *Rec. Trav. chim.*, 1947, **66**, 413.
[3] Bergmann and Blank, *J.*, 1953, 3786.
[4] Henne and deWitt, *J. Amer. Chem. Soc.*, 1948, **70**, 1548.
[5] Cox and McElvain, *Org. Synth.*, 1943, Coll. Vol. II, p. 279.
[6] Bergmann and Szinai, *J.*, 1956, 1521; Bergmann, Cohen, and Shahak, preceding paper.

liquid from which no trace of the barbituric acid could be isolated. Similar behaviour of 5-chlorobarbituric acid towards hydrobromic acid has been reported, though 5-bromobarbituric acid is claimed to be stable towards hydrochloric acid.[7] The barbituric acid could also not be obtained from fluoroacetylurea and oxalyl bromide, but it was prepared, in 16% yield, from ethyl fluoromalonate and urea in presence of sodium methoxide. 5-Fluoroalkylbarbituric acids have been described by Bruce and Huber [8] and by O'Neill and Pattison.[9]

Condensation of diethyl fluoromalonate with acetamidine gave 5-fluoro-4,6-dihydroxy-2-methylpyrimidine (III) and with guanidine gave 2-amino-5-fluoro-4,6-dihydroxypyrimidine (IV).

Experimental

Diethyl Difluoromalonate.[10]—Diethyl bromomalonate (300 g.), acetamide (100 g.) and potassium fluoride (113 g.) were heated at 160—170° under reflux with stirring for 1·5 hr., then distilled *in vacuo* to dryness. The distillate was washed repeatedly with water (to remove acetamide), dried (Na_2SO_4), and fractionated. Two fractions were obtained: (*a*) 90 g., b. p. 100—105°/23 mm., (*b*) 20 g., b. p. 110—140°/23 mm., mainly unchanged bromomalonate. Fraction (*a*) contained about 5% of fluorine, equiv. to about 16% of diethyl difluoromalonate. Fraction (*a*) (60 g.) in carbon tetrachloride (60 ml.) was heated with bromine (62 g.) as in the preparation of diethyl bromomalonate.[11] Distillation of the product yielded *diethyl difluoromalonate* (14 g.), b. p. 94—95°/23 mm., $\nu_{max.}$ (liquid film) 3000s, 1750vs, 1450s, 1310vs, 1220—1300vs,br, 1063vs, 1010vs, 840, 862s, 780 cm.$^{-1}$ (Found: F, 19·4. $C_7H_{10}O_4F_2$ requires F, 19·4%).

Difluoromalondiamide.—Diethyl difluoromalonate (5 g.) was treated with excess of concentrated aqueous ammonia, with occasional shaking, and the mixture kept overnight at 0°. The precipitated difluoromalondiamide (2 g., 57%), when washed with water and recrystallized from water, had m. p. 205—206° (lit., 206—207° [4], 200—201° [9]) $\nu_{max.}$ (KBr pellet) 3400, 3200, 1695 (all vs), 1620s, 1390s, 1290, 1130s, 1075s, 695 cm.$^{-1}$ (Found: C, 26·5; H, 3·2; N, 20·7. Calc. for $C_3H_4O_2N_2F_2$: C, 26·1; H, 2·9; N, 20·3%). When 20 g. of fraction (*a*) were treated with an excess of concentrated aqueous ammonia as above, a small amount of difluoromalondiamide, m. p. 205—206°, was obtained. The combined mother-liquors were evaporated to dryness and the residue was recrystallised from ethanol, to yield malonamide (3·5 g.), m. p. and mixed m. p. 169—171°.

Diethyl Fluoromalonate.—(*a*) Diethyl oxalofluoroacetate [12] (31 g.), with a few porcelain chips, was refluxed at 210—220° for 12 hr., then fractionated under reduced pressure. *Diethyl fluoromalonate* (9 g., 34%) had b. p. 121—122°/30 mm., n_D^{27} 1·4040 (Found: C, 47·2; H, 6·1; F, 11·2. $C_7H_{11}O_4F$ requires C, 47·2; H, 6·2; F, 10·7%), $\nu_{max.}$ (liquid) 3000, 1780, 1750 (all vs), 1474, 1455, 1380s, 1340vs, and 1280vs (C–F), 1170vs, 1070vs, 1090, 1040, 860, 790 cm.$^{-1}$.

(*b*) To a suspension of sodium methoxide (8·1 g.) in light petroleum (b. p. 50—70°; 100 ml.), ethyl fluoroacetate (15·9 g.) was added at 15—25° in small portions and with vigorous shaking (not stirring). After further 10 minutes' shaking, the sodio-derivative formed voluminous, yellow crystals. The mass was cooled at −10° and ethyl chloroformate (16·3 g.) in light petroleum (30 ml.) added as quickly as possible, but so that the temperature did not rise above 25°. The mixture was shaken for 1 hr. at room temperature, refluxed for 10 min. and decomposed with water (100 ml.). The organic layer was washed with 1% sodium hydrogen carbonate solution, dried ($MgSO_4$), and distilled through a short column, first at atmospheric pressure, then under 30 mm. The fraction boiling at 100—130°/30 mm. was redistilled under atmospheric pressure (204—205°) and had b. p. 121°/30 mm. (5·5—6·5 g., 20—25%) (Found: C, 47·8; H, 6·1; F, 10·8. Calc. for $C_7H_{11}O_4F$: C, 47·2; H, 6·2; F, 10·7%). A second fraction, b. p. 110—111°/2 mm. (2·4 g., 15%), was *diethyl α-fluoro-α-fluoroacetylmalonate* (Found: C, 46·0; H, 4·2; F, 16·2. $C_9H_{12}O_5F_2$ requires C, 45·4; H, 5·0; F, 16·0%).

(*c*) To the enol, prepared from ethyl fluoroacetate (53 g.) and sodium hydride (12 g.) in

[7] Biltz and Wittek, *Ber.*, 1921, **54**, 1035; Bock, *Ber.*, 1922, **55**, 3400.
[8] Bruce and Huber, *J. Amer. Chem. Soc.*, 1953, **75**, 4668.
[9] O'Neill and Pattison, *ibid.*, 1957, **79**, 1956.
[10] Inman, Oesterling, and Tyczkowski, *J. Amer. Chem. Soc.*, 1958, **80**, 6533.
[11] Palmer and McWherter, *Org. Synth.*, 1942, Coll. Vol. I, p. 245.
[12] Blank, Mager, and Bergmann, *J.*, 1955, 2190.

anhydrous ether (200 ml.), ethyl chloroformate (54·5 g.) in ether (50 ml.) was added at 0° with stirring during 15 min. The mixture was refluxed for 4 hr. and cold water added after 12 hr. The ethereal solution was dried and distilled. The diethyl fluoromalonate (19 g., 21%) was obtained, having b. p. 75—80°/4—5 mm., n_D^{28} 1·4032 (Found: C, 47·5; H, 6·2; F, 10·7%). Another fraction (8 g.) boiled at 110—111°/2 mm. after two distillations, and had n_D^{28} 1·4180. It was mainly ethyl α-fluoro-α-fluoroacetylmalonate, but contained a second substance poorer in fluorine, probably triethyl fluoromethanetricarboxylate; on hydrolysis with a slight excess of alcoholic potassium hydroxide at room temperature it gave crystalline dipotassium fluoromalonate. Treatment of an aqueous solution of this salt with 1 mol. of hydrochloric acid gave hydrated potassium hydrogen fluoromalonate, which, after recrystallisation from water, lost water when heated at 120—130° and decomposed at 180°, and on treatment with an excess of acid, followed by thorough extraction with ether, afforded fluoromalonic acid, m. p. 135—136° (lit.,[1] 135·8—136·5°). With concentrated aqueous ammonia, the higher-boiling fraction gave a product, m. p. 199° (from water), identified as *fluoromalondiamide*, by mixed m. p. (cf. below) and the *X*-ray powder diagram (Found: C, 30·2; H, 3·9; F, 15·9. $C_3H_5O_2N_2F$ requires C, 30·0; H, 4·2; F, 16·0%).

The formation of triethyl fluoromethanetricarboxylate was avoided and pure diethyl α-fluoro-α-fluoroacetylmalonate obtained when ethyl sodiofluoroacetate in ethereal suspension was *added to* the ethyl chloroformate.

Fluoromalondiamide, prepared by treating the pure ester with excess of aqueous concentrated ammonia, as described above, had m. p. 198—199° (from water), $\nu_{max.}$ (potassium bromide pellet) 3400, 3200, 1700 (all vs), 1450s, 1420vs, 1320s, 1115vs, 1075vs, 815, 795, 700s,br cm.$^{-1}$ (Found: C, 30·3; H, 4·2; N, 23·3; F, 15·8. Calc. for $C_3H_5O_2N_2F$: C, 30·0; H, 4·2; N, 23·3; F, 16·0%).

2-*Ethylthio*-5-*fluoro*-4,6-*dihydroxypyrimidine* (I).—A mixture of ethyl fluoromalonate (12 g.), *S*-ethylisothiouronium bromide (12·5 g.) and 2M-sodium methoxide (68 ml.) was kept at 28—30° for 4 days. The methanol was distilled off *in vacuo* and the residue dissolved in a little water and acidified with hydrochloric acid. Recrystallisation from aqueous alcohol gave the *product* (12 g., 95%), m. p. 215—220° (decomp.) (Found: C, 38·1; H, 4·1. $C_6H_7O_2N_2FS$ requires C, 37·9; H, 3·7%).

Fluoroacetylurea.[13]—Fluoroacetyl bromide [2] (40 g.), urea (17 g.), benzene (100 ml.), and concentrated sulphuric acid (1 drop) were refluxed with vigorous stirring for 12 hr. The solid (22 g., 65%) was filtered off, washed with benzene, digested with cold water, and collected. Crystallised from dimethylformamide, it had m. p. 216—218° (Found: C, 30·3; H, 4·3. $C_3H_5O_2N_2F$ requires C, 30·0; H, 4·2%).

With oxalyl bromide a solid product was obtained which, however, did not give 5-fluorobarbituric acid when heated in boiling tetrahydronaphthalene.

5-*Fluorobarbituric Acid* (II).—Urea (3 g.), ethyl fluoromalonate (9 g.), and M-sodium methoxide (50 ml.) were refluxed for 5 hr., then kept for 12 hr. A solid precipitate was filtered off, dissolved in a little water, and acidified with hydrochloric acid. 5-*Fluorobarbituric acid* crystallised and, recrystallised from glacial acetic acid, had m. p. >260° (decomp.) (1 g., 16%) (Found: C, 32·9; H, 2·1; F, 13·0. $C_4H_3O_3N_2F$ requires C, 32·9; H, 2·1; F, 13·0%).

5-*Fluoro*-4,6-*dihydroxy*-2-*methylpyrimidine* (III).—To a solution of acetamidine hydrochloride (2 g.) in 2M-methanolic sodium methoxide (20 ml.), diethyl fluoromalonate (3·5 g.) was added, and the mixture kept overnight. The solvent was removed under reduced pressure and the residue dissolved in a little water. On acidification with hydrochloric acid, the *product* (1·5 g., 53%) crystallised in fine prisms. It was purified by dissolution in dilute sodium hydroxide solution, treatment with charcoal, filtration, and acidification of the filtrate. It decomposed above 300° (Found: C, 41·5; H, 3·5; F, 12·4. $C_5H_5O_2N_2F$ requires C, 41·6; H, 3·5; F, 13·2%), and had $\lambda_{max.}$ (in ethanol) 262 mμ (log ε 3·96), $\nu_{max.}$ (in potassium bromide) 3410, 2800, 2700, 1680vs(CO), 1552, 1450, 1317, 1186, 1050 (C–F), 950, 780, 752 cm.$^{-1}$.

2-*Amino*-5-*fluoro*-4,6-*dihydroxypyrimidine* (IV).—Diethyl fluoromalonate (14 g.) and guanidine hydrochloride (7·5 g.) in 2M-sodium methoxide in methanol (80 c.c.) were kept at room temperature, with occasional shaking, for 48 hr., then evaporated under reduced pressure. The residue was taken up in water and acidified with hydrochloric acid. The precipitate was redissolved in sodium hydroxide solution, treated with charcoal until the filtrate was colourless,

[13] Cf. Stoughton, *J. Org. Chem.*, 1938, **2**, 514.

and precipitated with acid. After filtration and washing with water, alcohol and ether, the yield of *pyrimidine* was 5·5 g. (48%) (Found: C, 32·9; H, 3·0. $C_4H_4O_2N_2F$ requires C, 33·1; H, 2·8%).

This work was sponsored by the United States National Institute of Health.

DEPARTMENT OF ORGANIC CHEMISTRY, HEBREW UNIVERSITY, JERUSALEM.
SCIENTIFIC DEPARTMENT, MINISTRY OF DEFENCE,
TEL-AVIV, ISRAEL. [*Received, January 23rd*, 1959.]

---

668. *The Chemistry of the* Aristolochia *Species. Part IV.* The Structure of Aristolactone.*

By J. W. STEELE, J. B. STENLAKE, and W. D. WILLIAMS.

The sesquiterpenoid lactone, aristolactone, is shown to be βγ-unsaturated. Oxidation by chromic acid to succinic and acetic acid, and dehydrogenation of aristolactone derivatives to vetivazulene and a naphthalenic substance, led to the monocarbocyclic structure (I). This is supported by the properties of methyl oxoaristate and other aristolactone derivatives.

IN reporting our further work on aristolactone, we mention first a few miscellaneous observations. The yields of aristolactone from *Aristolochia reticulata* have been improved by chromatographing the petrol-soluble extract which remains after crystallisation of the lactone. The lactone has also been isolated from *A. serpentaria* Linn., but is not found in either *A. longa* Linn. or *A. indica* Linn. The re-arrangement of aristolactone to isoaristolactone described in Part II[1] has been re-examined: heating with a strong sulphonic acid resin in ethanol gave improved yields, and almost quantitative yields were obtained when aristolactone was treated with warm ethanolic sulphuric acid.

In our structural work we found ozonolysis of aristolactone and isoaristolactone to give formaldehyde (as dimedone derivative) in yields of 29% and 26·5%, respectively, based on two vinylidene substituents, compared with 36% for ethyl oxoaristate based on a single vinylidene substituent. The dihydro-lactone obtained from both aristolactone and isoaristolactone failed to yield formaldehyde on ozonolysis, indicating reduction and re-arrangement, respectively, of the vinylidene groups. The dihydro-lactone is now regarded as an isodihydroisoaristolactone, and not dihydroaristolactone as previously designated, since (*a*) its slow hydrolysis by ethanolic potassium hydroxide is characteristic of isoaristolactone and in contrast with that of aristolactone, (*b*) isodihydroisoaristolactone has $[\alpha]_D^{17}$ −77°, which is comparable with that of isoaristolactone ($[\alpha]_D^{17}$ −44°) and in contrast to that of aristolactone ($[\alpha]_D^{14}$ +156·4°), and (*c*) infrared spectra show a trisubstituted double bond (band at 815 cm.$^{-1}$ in carbon disulphide) in both isoaristolactone and isodihydroisoaristolactone, not evident with aristolactone. Hydrogenation of one vinylidene group in isoaristolactone is, therefore, accompanied by re-arrangement of the second vinylidene group to a trisubstituted ethylenic group, and reduction of aristolactone to isodihydroisoaristolactone is to be explained by re-arrangement of both the "lactone double bond" and the remaining vinylidene group. Similar re-arrangements are known,[2] and the steric requirements of such migrations induced by hydrogenation catalysts have been discussed.[3] The present conclusions are also supported by evidence of similar transformations in the reduction of the sesquiterpene reticulene,[4] which occurs with aristolactone in *A. reticulata* and *A. serpenteria*. Reticulene, which possesses two vinylidene substituents,

* Part III, *J.*, 1957, 4120.

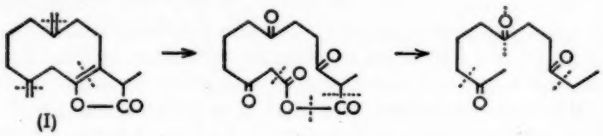
[1] Stenlake and Williams, *J.*, 1955, 2114.
[2] Irvine, Laurie, McNab, and Spring, *J.*, 1956, 2029; Howe and McQuillin, *J.*, 1956, 2670.
[3] Bream, Eaton, and Henbest, *J.*, 1957, 1974.
[4] Stenlake and Williams, *J. Pharm. Pharmacol.*, 1954, **6**, 1005.

XUM

yields dihydroisoreticulene on partial hydrogenation, by reduction of one vinylidene and re-arrangement of the other to a trisubstituted ethylenic group.[5]

Assignment of the lactone double bond as αβ was based on the assumption now disproved (above) that isodihydroisoaristolactone was formed by reduction of the lactone double bond, and not the vinylidene group. Re-examination of the ultraviolet absorption spectrum of aristolactone and isoaristolactone down to 198 mμ (a fused silica prism being used), and other evidence described below establish the lactone ring as βγ-unsaturated. This does not conflict with our interpretation of the alkaline re-arrangement to methyl and ethyl oxoaristate and, further, provides a more satisfactory explanation of the fractional iodine values found for aristolactone[1] (cf. Cavallito and Haskell[6]). It also explains the failure of aristolactone to respond to the Legal test, and its failure to form an ammonia adduct.[1] Hydrogenolysis with the formation of acidic products during hydrogenation of aristolactone in acid solution (hydrogen uptake 4 mols.) also supports the βγ-unsaturated γ-lactone formulation.[7]

The carbon skeleton of aristolactone, for which we now propose structure (I), was suggested by dehydrogenation with palladium–charcoal. Experiments with aristolactone, isohexahydroisoaristolactone,* and other crystalline derivatives failed, but the oily products remaining after the preparation of isohexahydroisoaristolactone, dihydroxyaristolactone, isoaristolactone, and methyl oxoaristate (all from pure crystalline lactone) all gave a violet azulene (in poor yield) and, in one instance, a trace of a naphthalenic derivative. The ultraviolet and visible absorption spectra of the azulene and of its azulenium ion (in 50% sulphuric acid) were virtually identical with the corresponding spectra of vetivazulene (2-isopropyl-4,8-dimethylazulene)[8]. Although formation of vetivazulene from uncharacterised intermediates is inconclusive, the preparation of these intermediates, in every case from either pure crystalline aristolactone or crystalline lactone derivatives, implies an element of skeletal relation between the latter and vetivazulene. Production of vetivazulene and naphthalenic products from monocyclic parent structures does not exclude skeletons of the elemol[9] (III) and possibly also the xanthanin type (IV), though no aromatic dehydrogenation products have, in fact, been obtained from xanthinin.[10] But, considered with the other evidence (below), it suggests that structure (I), based on a cyclodecane skeleton which conforms to the isoprene rule, offers the most satisfactory explanation of the properties of aristolactone.



(I)

In support of structure (I), vigorous oxidation of aristolactone with potassium dichromate and sulphuric acid gave formic acid (trace) and acetic acid (1·6 mol.); the non-volatile residue gave succinic acid, confirmed as its *S*-benzylthiuronium salt, in agreement with the annexed degradation of structure (I), which, despite the presence of only one *C*-methyl group, permits the formation of 2 mol. of acetic acid. Paper chromatography

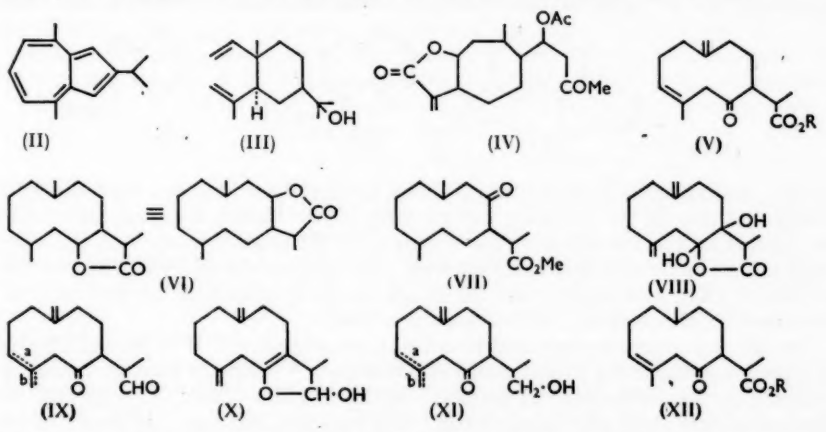
* The change in nomenclature from hexahydroaristolactone to isohexahydroisoaristolactone follows from the fact that it is formed from isodihydroisoaristolactone.

[5] Coutts, Stenlake, and Williams, unpublished work.
[6] Cavallito and Haskell, *J. Amer. Chem. Soc.*, 1946, **68**, 2332.
[7] Jacobs and Scott, *J. Biol. Chem.*, 1930, **87**, 601; 1931, **93**, 139.
[8] Susz, Pfau, and Plattner, *Helv. Chim. Acta*, 1937, **20**, 469; Sörensen and Hougen, *Acta Chem. Scand.*, 1948, **2**, 447; Chopard-dit-Jean and Heilbronner, *Helv. Chim. Acta*, 1952, **35**, 2170.
[9] Sykora, Hérout, and Šorm, *Coll. Czech. Chem. Comm.*, 1955, **20**, 220.
[10] Geissman and Deuel, *Chem. and Ind.*, 1957, 328; *J. Amer. Chem. Soc.*, 1957, **79**, 3778; Geissman, Deuel, Bonde, and Addicott, *ibid.*, 1954, **76**, 685; Dolejs, Hérout, and Šorm, *Coll. Czech. Chem. Comm.*, 1958, **23**, 504.

of the mother-liquors in a phenol–formic acid system gave well-defined spots of succinic acid, and showed the complete absence of glutaric and higher dibasic acids, as expected.

Evidence for three double bonds in aristolactone (I) rests on reduction of the lactone and of methyl oxoaristate (V; R = Me) to isohexahydroisoaristolactone (VI) and the oily methyl tetrahydro-oxoaristate (VII) respectively, and on the determination of bromine numbers.[1] Re-determination of bromine numbers for aristolactone, its derivatives, and a series of control compounds (Table 2, p. 3299) shows that both reaction time and solvent are critical. Unhindered double bonds react quantitatively in carbon tetrachloride within two minutes (compounds 1 and 2) but, under the same conditions, hindered double bonds give fractional values (compound 5), whilst cyclopropane rings undergo negligible reaction (compounds 6 and 7). Results for 6,7-dihydroxyaristolactone (VIII) (compound 10) and iso-oxoaristaldehyde (IX) (compound 11), which lack the hindered lactone double bond of aristolactone, indicate two double bonds. Aristolactone (I) reacts with 2·6 mol. of perbenzoic acid in 48 hr., in conformity with the presence of three double bonds.

The lactone double bond was confirmed as $\beta\gamma$ by reduction of aristolactone (I) with lithium aluminium hydride, which gave two products depending upon the conditions. At 0° a crystalline product was obtained, which is probably the γ-keto-aldehyde (IX), $[\alpha]_D$ +82°, formed by re-arrangement of the intermediate hemiacetal [11] (X). Compound (IX) gave a positive Schiff's reaction, reduced ammoniacal silver nitrate (aldehyde), and showed end-absorption in the ultraviolet region (ε 3234 at 210 mμ) with a secondary band of absorption and low-intensity maximum at 284 mμ (ε 58; aldehyde and ketone). The infrared spectrum (potassium bromide disc) showed bands confirming the vinylidene absorption (904 and 1645 cm.$^{-1}$) and a single broad band in the carbonyl stretching region with a peak at 1752 cm.$^{-1}$ (1746 cm.$^{-1}$ in chloroform). The latter band, unlike the carbonyl bands of methyl oxoaristate, is not resolved, and, moreover, is not typical of the proposed oxocyclodecan-aldehyde structure. The reason for this anomaly is not clear and further investigations are in prospect. More vigorous reduction with lithium aluminium hydride gave the 1,4-ketol, oxoaristoöl (XI), which showed end-absorption in the ultraviolet spectrum [ε 3860 at 210 mμ (vinylidene), and a shoulder at 280 mμ (ketone)].



(II) (III) (IV) (V) (VI) (VII) (VIII) (IX) (X) (XI) (XII)

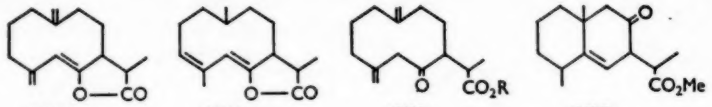
On the basis of structure (I), methyl and ethyl oxoaristate, the products of re-arrangement with cold methanolic or ethanolic alkali,[1] can be assigned structures (V; R = Me and Et, respectively). Ozonolysis of ethyl oxoaristate gave formaldehyde, confirming the presence of a vinylidene group, whilst a trisubstituted double bond is indicated by an infrared band at 815 cm.$^{-1}$ not present in aristolactone. Careful hydrogenation of methyl

[11] Arth, *J. Amer. Chem. Soc.*, 1953, **75**, 2413; Dietrich, Lederer, and Mercier, *Annalen*, 1957, **603**, 8.

oxoaristate at a platinum catalyst gave, after the uptake of 1 mol., a new crystalline γ-keto-ester, methyl dihydro-oxoaristate (XII; R = Me), in which the vinylidene group had been reduced, as shown by the absence of formaldehyde after ozonolysis.

Reduction of the vinylidene group of methyl oxoaristate is accompanied by a marked fall in absorption intensity at 209 mμ ($\Delta\varepsilon$ 4040). Comparable $\Delta\varepsilon$ values for the reduction of ethyl oxoaristate (V; R = Et) to ethyl dihydro-oxoaristate (XII; R = Et), and of isoaristolactone (XIII) to isodihydroisoaristolactone (XIV) are 3430 and 3400 respectively. The last two reductions both concern vinylidene groups, since neither product yields formaldehyde on ozonolysis. This unexpectedly large vinylidene contribution to the end-absorption invalidates the previous assumption [1] of a tetrasubstituted double bond in methyl oxoaristate. The presence of a trisubstituted double bond in methyl dihydro-oxoaristate has now been demonstrated by (*a*) a yellow colour with tetranitromethane, (*b*) catalytic reduction to methyl tetrahydro-oxoaristate (VII) (hydrogen uptake 1 mol.), (*c*) end-absorption in the ultraviolet (ε 2300 at 209 mμ), (*d*) an infrared band at 815 cm.$^{-1}$ (potassium bromide disc), and (*e*) ozonolysis to a product having a positive nitroprusside reaction for methyl ketone (not given by methyl dihydro-oxoaristate), which, however, was not the expected diketonic acid, $C_{16}H_{26}O_6$, but instead a weakly acidic substance, $C_{16}H_{24}O_5$, formed apparently by loss of the elements of water during distillation. This product, which was not characterised, showed pH- and concentration-dependent absorption in the ultraviolet region (Table 1, p. 3297). Its formation, however, without loss of carbon establishes the ozonised double bond as part of a cyclic system.

It might be expected, by analogy with the reduction of isoaristolactone (XIII) to isodihydroisoaristolactone (XIV), that the trisubstituted double bond in methyl dihydro-oxoaristate (XII; R = Me) also arises from a methyl oxoaristate of structure (XV) by re-arrangement at the reduction stage. Both methyl and ethyl oxoaristate, however, show an infrared band at 815 cm.$^{-1}$ (in carbon disulphide), in support of the alternative structure (V). Moreover, the divinylidene structure (XV) is excluded further by a comparison of molecular models. These reveal the improbability of a ten-membered ring with three exocyclic multiple bonds, for which the only conformations are those with an unduly high proportion of unfavourable methylene conformations. In contrast, the virtually



(XIII) (XIV) (XV) (XVI)

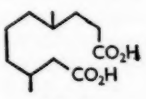
strainless conformation(s) of structure (V) with one endocyclic and two exocyclic multiple bonds would provide the necessary driving force for the further re-arrangement which is now implied in the formation of the oxoaristates (V) from aristolactone (I). Similar considerations apply also to oxoaristaldehyde (VI), iso-oxoaristaldehyde (IX; see below), and aristoöl (XI), and suggest that the structures (IXa) and (XIa) are preferable to the alternatives (b) although no direct evidence is available.

The carbonyl groups in both methyl and ethyl oxoaristate (V; R = Me and Et) showed the typical non-reactivity expected of cyclodecanones,[12] failing to form an oxime, semicarbazone, or 2,4-dinitrophenylhydrazone. Methyl dihydro- (XII; R = Me) and tetrahydro-oxoaristate (VII) also failed to react with carbonyl reagents. Attempts to reduce the carbonyl group of methyl tetrahydro-oxoaristate with aluminium isopropoxide were also unsuccessful, and consistently the carbonyl group in oxoaristaldehyde (IX) resisted reduction with lithium aluminium hydride under normal conditions. That the non-reactivity of these compounds is due to an " O-inside " conformation of the cyclodecane carbonyl group rather than hindrance of the adjacent methyl and methoxycarbonyl

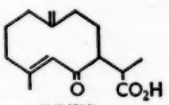
[12] Prelog, *J.*, 1950, 420.

substituents is established by comparison with the analogous methyl 8-oxosanta-5-enoate [13,14] (XVI) which readily forms a crystalline 2,4-dinitrophenylhydrazone.[13] Further, methyl dihydro-oxoaristate (XII; R = Me) shows a carbonyl band in the infrared spectrum at 1693 (in potassium bromide) and 1698 cm.$^{-1}$ (in chloroform) typical of large-ring ketones.[15] Methyl oxoaristate similarly shows carbonyl absorption at 1693 cm.$^{-1}$ (in potassium bromide).

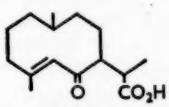
Ring cleavage of methyl tetrahydro-oxoaristate (VII) by nitric acid gave a saturated (and therefore acyclic) dibasic acid $C_{12}H_{22}O_4$, isolated as the silver salt. Although not characterised as the expected 4,8-dimethylsebacic acid (XVII), this product is consistent with the large-ring ketone structure. Moreover, paper chromatography of the oily oxidation product showed no evidence of small fragments, such as α-methyladipic acid, which might be expected to arise from a cyclohexane derivative.



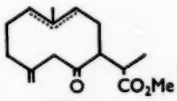
(XVII)



(XVIII)



(XIX)



(XX)

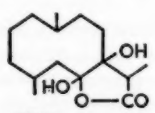
The two non-lactonic double bonds in aristolactone (I) were located by the action of alkali on methyl oxoaristate (V; R = Me) and methyl dihydro-oxoaristate (XII; R = Me). The former, when refluxed with methanolic potassium hydroxide, gave a crystalline iso-oxoaristic acid (XVIII), $[\alpha]_D$ −3·45°, which exhibited an ultraviolet absorption maximum at 243 mμ (ε 6780), in agreement with the calculated wavelength (239 mμ) for an αβ-unsaturated ketone with two β-substituents.[16] Methyl dihydro-oxoaristate (XII; R = Me), treated similarly with alkali, gave an oily product (XIX), which also showed an ultraviolet absorption maximum at 245 mμ (ε 6300). This confirms that it is the trisubstituted double bond and not the vinylidene group of methyl oxoaristate that is βγ to the carbonyl group, and thereby excludes the alternative structures (XX) for methyl oxoaristate.

Aristolactone (I) with potassium permanganate in acetone gave 6,7-dihydroxyaristolactone (VIII). The latter is doubly unsaturated (bromine number 1·90), is readily hydrogenated to tetrahydrodihydroxyaristolactone (XXI), and exhibits end-absorption in the ultraviolet region (ε 3200 at 210 mμ) consistent with retention of the vinylidene double bonds. Both 6,7-dihydroxyaristolactone and its tetrahydro-derivative show an infrared band at 1767 cm.$^{-1}$ (in chloroform) typical of a saturated γ-lactone. The 1,2-glycol link was demontrated in tetrahydro-6,7-dihydroxyaristolactone (XXI) by oxidation with sodium bismuthate,[17] although the oily product gave only an amorphous 2,4-dinitrophenylhydrazone which was unstable and resisted characterisation. 6,7-Dihydroxyaristolactone (VIII) showed an infrared band at 906 cm.$^{-1}$ (in potassium bromide; vinylidene), failed to yield formaldehyde with sodium metaperiodate,[18] and did not re-arrange in acid solution (see below). A second product of the permanganate oxidation of aristolactone, an acidic oil, gave succinic acid as the only characterisable product when the oxidation was continued.

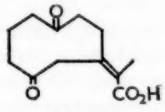
Acid-catalysed re-arrangement of aristolactone (I) to isoaristolactone (XIII), which results from migration of the lactone double bond,[1] is seen as a shift from a less stable βγ-endocyclic position to the more stable γδ-exocyclic position.[19] Conversion of isoaristolactone by lithium aluminium hydride at 0° into iso-oxoaristaldehyde, $[\alpha]_D$ −50·1°,

[13] Ukita and Nakazawa, *Pharm. Bull.* (*Japan*), 1954, **2**, 299.
[14] Asselineau and Bory, *Compt. rend.*, 1958, **246**, 1874.
[15] Šorm, Dolejs, and Pliva, *Coll. Czech. Chem. Comm.*, 1950, **15**, 186.
[16] Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76.
[17] Rigby, *J.*, 1950, 1907.
[18] Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1476.
[19] Brown, Brewster, and Shechter, *ibid.*, 1954, **76**, 467.

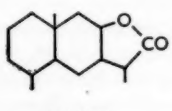
stereoisomeric with oxoaristaldehyde (IX), establishes the direction of double-bond shift to be as indicated. The stability of 6,7-dihydroxyaristolactone to acid under similar conditions (above) not only identifies the locus of re-arrangement, but also establishes that this is confined to a shift of the lactone double bond. Oxidation of isoaristolactone with chromic acid yields succinic acid as the largest identifiable fragment in accordance



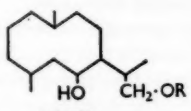
(XXI)



(XXII)



(XXIII)



(XXIV)

with structure (XIII), but the ultraviolet absorption spectrum does not show the expected intense maximum for the postulated diene system.[20] Molecular models, however, reveal that the two double bonds are non-coplanar in the only strainless conformations for the 1,3-diene system of isoaristolactone and for the cyclodeca-1,3-diene of isodihydroisoaristolactone, and depression of absorption intensities to the small maxima observed [1] at 272 mμ in isoaristolactone (ε 640) and isodihydroisoaristolactone (ε 606) accords with this lack of coplanarity in the diene system.[21] The diene structure is supported by the significantly greater end-absorption of isoaristolactone (ε 16,280 at 204 mμ) compared with that of aristolactone (ε 12,000 at 206 mμ), when examined with fused silica optics.

Ozonolysis of aristolactone gave formaldehyde as the sole volatile product. Decomposition of the ozonide with water or zinc and glacial acetic acid, or by catalytic reduction, gave acidic oils which were rapidly discolored by alkali, even at room temperature. Paper chromatography of the acidic product with (*a*) butan-1-ol–pyridine–water–ethanol and (*b*) pyridine–water–ammonia showed the presence of two keto-acids A [R_F 0·62 in (*a*) and 0·80 in (*b*)] and B [R_F 0·31 in (*a*) and 0·45 in (*b*)]. Oxidative hydrolysis of the ozonide gave the oily unsaturated ketonic acid, B, which showed end-absorption ($E^{1\%}_{1\,cm.}$ 250 at 210 mμ) and saturated ketone absorption at 275 mμ ($E^{1\%}_{1\,cm.}$ 5·6). The product gave no ferric chloride reaction, was readily decarboxylated on distillation to an unsaturated neutral oil (which showed end-absorption in the ultraviolet spectrum and gave analyses approximating to $C_{11}H_{16}O_2$), and underwent rapid ozonolysis to acetaldehyde (identified as its 2,4-dinitrophenylhydrazone and dimedone derivatives), in accord with the tentative structure (XXII).

The close structural relation between isohexahydroisoaristolactone (VI) and tetrahydroalantolactone [22] (XXIII) is borne out by a remarkable similarity in the infrared spectrum of the two compounds. We have, however, been unable to establish a link with the fully saturated lactone also of structure (VI) obtained by Suchy, Horak, Hérout, and Šorm,[23] by degradation of arctiopicrin. This lactone, derived from a crystalline keto-lactonic precursor, was liquid, and no optical rotation was reported, so that comparison with the presumed stereoisomeric isohexahydroisoaristolactone was not possible. Reduction of the liquid lactone with lithium aluminium hydride was reported to give a crystalline diol, m. p. 117° (XXIV; R = H), the monobenzoate (m. p. 89°) of which yielded, on oxidation, the corresponding 6-keto-12-benzoate for which no characteristics other than the infrared carbonyl frequency were given.[23] Similar reduction of isohexahydroisoaristolactone, however, afforded an almost quantitative yield of an isomeric crystalline diol, tetrahydroisoaristo-6,12-diol, m. p. 106—107°, $[\alpha]_D$ +18·7°, the 12-monobenzoate (XXIV; R = Bz) of which was obtained only as an oil, $[\alpha]_D$ +1·9°. No definite conclusion can

[20] Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd edn., Reinhold Publ. Corp., 1949, p. 185.
[21] Braude and Nachod, "Determination of Organic Structures by Physical Methods," Academic Press Inc., 1955, p. 169; Braude and Gofton, *J.*, 1957, 4270.
[22] Tsuda, Tanabe, Iwai, and Funakoshi, *J. Amer. Chem. Soc.*, 1957, **79**, 1009.
[23] Suchy, Horak, Hérout, and Šorm, *Chem. and Ind.*, 1957, 894.

therefore be reached concerning the identity or non-identity of the two lactones and their derivatives.

Stereochemical relations of aristolactone derivatives will be discussed in a later paper.

Experimental

Unless otherwise stated, rotations refer to solutions in absolute ethanol in a 1 dcm. tube, and ultraviolet absorption spectra to solutions in absolute ethanol, determined on a Hilger Uvispek spectrophotometer. We are indebted to Mr. W. McCorkindale and Dr. A. C. Syme for the microanalyses.

Aristolactone.—(*a*) This was isolated from the light petroleum-soluble extract of *Aristolochia reticulata* by seeding and crystallisation as described in Part I.[4] Chromatography of the residual oil in light petroleum (b. p. 40—60°) on a column of mixed activated charcoal (1 part) and Whatman standard grade cellulose powder (3 parts), and elution with the same solvent, gave a small lævorotatory fraction, followed by a strongly dextrorotatory fraction, from which a further yield of aristolactone, m. p. 110—111°, crystallised (total yield, 15 g. from 9·5 kg.).

(*b*) Extraction of *Aristolochia serpentaria* Linn. (4·5 kg.) as described above yielded 7·9 g. of aristolactone.

(*c*) Perbenzoic acid titration, showed double-bond equivalents of 2·28 (after 6 hr.), 2·56 (after 24 hr.), and 2·63 (after 48 hr.).

Ozonolysis of Aristolactone.—(*a*) Aristolactone (1·64 g.) was ozonised in dry chloroform (30 ml.) at 0° for 3 hr. The solvent was evaporated at room temperature, and the glassy ozonide refluxed for 3 hr. with 0·1N-hydrochloric acid (10 ml.), 30% hydrogen peroxide (10 ml.), and water (30 ml.). The oily suspension was extracted with chloroform, and the latter dried (Na_2SO_4) and evaporated to give a pale yellow acidic oil (0·83 g.) (Found: equiv., 224), $\lambda_{max.}$ 275 mμ ($E^{1\%}_{1\,cm.}$ 5·6), end absorption at 210 mμ ($E^{1\%}_{1\,cm.}$ 250).

The aqueous liquor, which gave a strongly positive sodium nitroprusside reaction for methyl ketone, was concentrated by freeze-drying, neutralised with sodium hydroxide, and distilled. The distillate gave an orange 2,4-dinitrophenylhydrazone, which when chromatographed on alumina gave two small unidentified fractions, m. p. 162—164° and 152—154° severally.

Ozonolysis of the chloroform-soluble oil from the above ozonolysis for a further 1½ hr., with decomposition and extraction as described, gave a viscous oil (0·25 g.). Distillation of the remaining aqueous liquors into an acid 50% ethanolic solution of 2,4-dinitrophenylhydrazine yielded acetaldehyde 2,4-dinitrophenylhydrazone, m. p. 147°, undepressed on admixture with authentic material (m. p. 149°) (Found: C, 42·7; H, 3·2; N, 24·9; O, 29·1. Calc. for $C_8H_8O_4N_4$: C, 42·9; H, 3·6; N, 25·0; O, 28·5%). Distillation into saturated aqueous dimedone gave acetaldehyde dimedone derivative, m. p. 131—134°, mixed m. p. with authentic material 132—135°.

(*b*) Aristolactone was ozonised in chloroform, the ozonide decomposed with hydrochloric acid and hydrogen peroxide as described above, and the oily fraction distilled to yield a colourless neutral oil (Found: C, 73·8; H, 10·1. $C_{11}H_{16}O_2$ requires C, 73·3; H, 9·0%). This was presumed to be 7-ethylidenecyclononane-1,5-dione.

(*c*) Aristolactone (415 mg.) was ozonised in chloroform, and the ozonide solution decomposed with zinc powder (0·4 g.) and glacial acetic acid (2 ml.). The aqueous extract was neutralised and finally made faintly acid with acetic acid. Addition of dimedone (0·5 g.) in 50% ethanol (20 ml.) gave formaldehyde–dimedone derivative (308 mg.; 29% calc. for two vinylidene groups), m. p. and mixed m. p. 190—191°.

Isoaristolactone.—(*a*) Aristolactone (0·1 g.) in 95% ethanol (10 ml.) was refluxed with activated Zeo-Karb-225 (1 g.) until the optical rotation had reached a constant negative value (*ca.* 9 hr.). Evaporation of the solvent gave isoaristolactone, m. p. 90—91° (35 mg.; from light petroleum).

(*b*) Aristolactone (50 mg.) in 99% ethanol (3 ml.) was mixed with a 10% solution (1 ml.) of sulphuric acid in 50% ethanol, warmed to 40° for 2 min., and allowed to cool. The crystalline product, obtained by adding water dropwise, gave isoaristolactone (40 mg.; from aqueous ethanol), m. p. 89·5—90° (block), $[\alpha]_D^{20}$ −42°.

(*c*) Aristolactone (490 mg.) in 99% ethanol (10 ml.) was mixed with a 10% solution (40 ml.) of sulphuric acid in 50% ethanol at room temperature and the reaction followed polarimetrically. When the optical rotation reached a constant negative value (5 hr.), dilution with water gave

colourless needles of isoaristolactone (430 mg.; 86% from aqueous ethanol), m. p. 90—91° (block), $\nu_{max.}$ (in potassium bromide disc) at 1742 (unsaturated γ-lactone), 902 and 1641 (vinylidene), and 824 cm.$^{-1}$.

Ozonolysis of Isoaristolactone.—Isoaristolactone (153 mg.) was ozonised in chloroform (15 ml.) at −7°, and the solution treated with glacial acetic acid (2 ml.) and zinc powder (0·4 g.), added gradually (10 min.). The solution was filtered, extracted with water (4 × 20 ml.), neutralised, and treated with dimedone (350 mg.) in ethanol (20 ml.), to give formaldehyde–dimedone derivative (103 mg., 26·5% calc. yield for two vinylidene groups), m. p. and mixed m. p. 183—187°.

Ozonolysis of Isodihydroisoaristolactone.—Isodihydroisoaristolactone (176 mg.) was ozonised in chloroform (5 ml.), and the ozonide decomposed as described for isoaristolactone. The aqueous extract gave no precipitate when treated with dimedone or when distilled into an acid solution of 2,4-dinitrophenylhydrazine.

Chromic Acid Oxidation of Aristolactone.—Aristolactone (476 mg.) was warmed cautiously with a cooled mixture of potassium dichromate (4·5 g.), sulphuric acid (4 ml.) and water (10 ml.). After reaction had subsided, the mixture was refluxed gently for 2 hr., then steam-distilled. The distillate required 5·8 ml. of 0·5N-sodium hydroxide for neutralisation (equiv. to 1·6 mol.) and gave crystalline sodium acetate on evaporation, identified by ferric chloride reaction (red) and by conversion into *S*-benzylthiuronium acetate, m. p. 141—142° (from aqueous ethanol) undepressed on admixture with authentic material, m. p. 143—144°.

Non-volatile products were extracted with ether (6 × 50 ml.), and the extracts were dried (Na_2SO_4) and evaporated to yield a semicrystalline residue. Recrystallisation from light petroleum–ethanol and then ether gave succinic acid, m. p. and mixed m. p. 183—185°. The acid gave *S*-benzylthiuronium succinate, m. p. and mixed m. p. 153—154°.

The residue from the mother-liquors was chromatographed in No. 1 Whatman filter paper by the ascending technique, with phenol–formic acid–water (80 : 1 : 19), and the paper was sprayed with Bromocresol Green. Drying showed two yellow (acidic) spots, of R_F 0·71 (succinic acid, as shown by comparison with an authentic sample) and R_F 0·99. The latter acid was not identified, but was shown to possess a carbonyl group by spraying with an acid solution of 2,4-dinitrophenylhydrazine.

Chromic Acid Oxidation of Isoaristolactone.—Isoaristolactone (500 mg.) was gently refluxed for 2 hr. with potassium dichromate (4·5 g.), water (10 ml.) and sulphuric acid (4 ml.). Steam-distillation gave acetic acid. Non-volatile products were extracted with ether, and the ethereal solution was evaporated. The residue, washed with chloroform, yielded succinic acid, m. p. 183—185°, R_F 0·75 (phenol–formic acid–water, 80 : 1 : 19). The mother-liquors were partitioned in chloroform on a buffered (pH 7·4) silica gel column to yield an acidic oil, R_F 0·97 (phenol–formic acid–water, 80 : 1 : 19), R_F 0·90 (butan-1-ol–formic acid–water, 10 : 3 : 10); distillation gave a semicrystalline product which could not be characterised.

Oxoaristaldehyde (IX).—Aristolactone (520 mg.) was added portionwise to lithium aluminium hydride (125 mg.) in sodium-dried ether (15 ml.) at 0° during 10 min. After a further 5 min. the solution was allowed to warm to room temperature. Excess of reagent was destroyed by water (1 drop), and the solution treated with dilute hydrochloric acid and extracted with ether. The ethereal solution, when dried (Na_2SO_4) and evaporated, gave an oil (500 mg.) which gave colourless needles of *oxoaristaldehyde*, m. p. 197—198° (block) (from acetone), $[\alpha]_D^{16\cdot5}$ +82° (*c* 0·48), $\lambda_{max.}$ 284 (ε 58), end-absorption at 210 mμ (ε 3234) (Found: C, 76·9; H, 9·25. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%). This reduced ammoniacal silver nitrate and restored the colour to Schiff's reagent.

Attempted Isomerisation of Oxoaristaldehyde.—Oxoaristaldehyde (90 mg.) was dissolved in a 10% solution (8 ml.) of sulphuric acid in 50% ethanol, and the optical rotation observed during 6 hr. No change was observed, and oxoaristaldehyde, m. p. 197—198°, was recovered.

Oxoaristoöl.—Aristolactone (120 mg.) was added portionwise during 10 min. to lithium aluminium hydride (39 mg.) in dry ether (5 ml.) at room temperature, and the mixture refluxed gently for 5 min. Excess of reagent was destroyed by water, and the solution treated with dilute hydrochloric acid, and extracted with ether. The ethereal solution was dried (Na_2SO_4) and evaporated, yielding a colourless oil, which crystallised from acetone to give colourless needles of *oxoaristoöl* (10 mg.), m. p. 245—246°, $\lambda_{max.}$ 270—275 mμ (ε about 184), end-absorption at 210 mμ (ε 3860) (Found: C, 76·5; H, 10·0. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%).

Iso-oxoaristaldehyde (IX).—Isoaristolactone (400 mg.) in sodium-dried ether (25 ml.) was

reduced with lithium aluminium hydride (60 mg.) as described for aristolactone; it yielded *iso-oxoaristaldehyde* (40 mg.; from methanol), m. p. 211—213° (block), $[\alpha]_D^{20}$ −50·1° (*c* 0·40 in chloroform), $\lambda_{max.}$ 290 mμ (ε 30), end-absorption at 209 mμ (ε 4960) (Found: C, 77·4; H, 9·3. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%), $\nu_{max.}$ 1753 cm.$^{-1}$ (C=O) in chloroform. This aldehyde reduced warm ammoniacal silver nitrate and restored the colour to Schiff's reagent.

Methyl Dihydro-oxoaristate.—Methyl oxoaristate (1 g.) in ethanol (25 ml.) was shaken with platinum oxide (0·1 g.) in presence of hydrogen, until 1 mol. was absorbed. Filtration and evaporation gave colourless *methyl dihydro-oxoaristate* (0·9 g.), m. p. 68—68·5° (block) (from 60% ethanol), $[\alpha]_D^{15}$ +152° (*c* 0·788), $\lambda_{max.}$ 290 mμ (ε 160), end-absorption at 210 mμ (ε 3600), $\nu_{max.}$ (in KBr disc) 815 (trisubstituted double bond), 1732 (ester C=O) and 1693 cm.$^{-1}$ (ketone), (in chloroform) 1728 (ester C=O) and 1698 cm.$^{-1}$ (ketone) (Found: C, 71·8; H, 9·8. $C_{16}H_{26}O_3$ requires C, 72·1; H, 9·8%). The product gave a yellow colour with tetranitromethane.

Ethyl Dihydro-oxoaristate.—Ethyl oxoaristate (281 mg.), hydrogenated as above, gave colourless needles of *ethyl dihydro-oxoaristate*, m. p. 65—66° (from ethanol, after sublimation), $[\alpha]_D^{17}$ +131° (*c* 1·21), $\lambda_{max.}$ 287 mμ (ε 52), end-absorption at 208 mμ (ε 3570) (Found: C, 72·8; H, 10·1. $C_{17}H_{28}O_3$ requires C, 73·2; H, 10·2%), giving a yellow colour with tetranitromethane.

Ozonolysis of Ethyl Oxoaristate.—Ethyl oxoaristate (290 mg.) in chloroform (10 ml.) was treated with ozonised oxygen at 0°. The ozonide obtained on evaporation of the solvent was decomposed by the addition of water. The solution was kept overnight, then distilled, and the distillate was treated with dimedone (500 mg.) in 30% ethanol (20 ml.) to give formaldehyde–dimedone derivative (112 mg., 36% calc. on one vinylidene group), m. p. and mixed m. p. 188—190°. Distillation of the aqueous filtrate gave a small amount of a 2,4-dinitrophenylhydrazone, m. p. 130—134° (from ethanol), insufficient for characterisation. The residual non-volatile oil (260 mg.) had equiv. 228 and $\lambda_{max.}$ 280 mμ ($E^{1\%}_{1\,cm.}$ 14·2), and gave positive reactions with alkaline sodium nitroprusside (methyl ketone) and ammoniacal silver nitrate, but was not characterised.

Ozonolysis of Ethyl Dihydro-oxoaristate.—Ethyl dihydro-oxoaristate (100 mg.) was ozonised as described for isoaristolactone. The resulting aqueous solution gave no colour with Schiff's reagent and no precipitate with dimedone. The oily residue from the chloroform solution gave a positive reaction with alkaline sodium nitroprusside for methyl ketone.

Ozonolysis of Methyl Dihydro-oxoaristate.—Methyl dihydro-oxoaristate (1·37 g.) was ozonised as described for methyl oxoaristate. The aqueous distillate failed to react with 2,4-dinitrophenylhydrazine. The non-volatile residue extracted with chloroform and distilled gave a pale yellow oil (0·58 g.), b. p. 220—240°/0·4 mm. (Found: C, 65·3; H, 8·6. $C_{16}H_{24}O_5$ requires C, 64·8; H, 8·2%. This product, gave a yellow colour with tetranitromethane (unsaturation), a red colour with alkaline sodium nitroprusside (methyl ketone) and showed the ultraviolet absorptions recorded in Table 1.

The oil (0·27 g.), when treated in 2N-sodium carbonate (20 ml.) at 50° with 3% potassium permanganate solution during 2 hr., gave, after filtration, acidification, and ether-extraction,

TABLE 1.

Concn. (%)	pH	$\lambda_{max.}$	$E^{1\%}_{1\,cm.}$	$\lambda_{max.}$	$E^{1\%}_{1\,cm.}$	Concn. (%)	pH	$\lambda_{max.}$	$E^{1\%}_{1\,cm.}$	$\lambda_{max.}$	$E^{1\%}_{1\,cm.}$
0·0038	1·43	238	250	289	212	0·0038	11·58	249	184	—	—
0·0038	5·80	240	200	289	184	0·00152	5·80	240	164	292	167
0·0038	10·20	249	187	290	167						

a pale yellow oil (0·18 g.). Treatment of the latter with diazomethane yielded a mobile liquid (76 mg.) (Found: C, 67·2; H, 9·4. $C_{15}H_{24}O_4$ requires C, 67·10; H, 9·0%).

Attempted Reduction of Methyl Tetrahydro-oxoaristate.—Methyl tetrahydro-oxoaristate (1·5 g.) in dry propan-2-ol (25 ml.) was refluxed for 6 hr. with aluminium isopropoxide (1 g.). No acetone was produced and methyl tetrahydro-oxoaristate (1·4 g.) was recovered.

Oxidation of Methyl Tetrahydro-oxoaristate.—Methyl tetrahydro-oxoaristate (0·7 g.) in ether was treated with concentrated nitric acid (5 ml.), the mixture being kept at 60° until evolution of nitrous fumes had ceased. Extraction with ether, and treatment of the solution with ammonia, gave an aqueous solution of a dibasic acid, which when chromatographed on Whatman No. 1 paper, with butan-1-ol–formic acid–water (10 : 3 : 10), ran ahead of pimelic acid almost on the solvent front (R_F 0·97). Treatment of the solution with silver nitrate gave colourless *silver 3,7-dimethyldecanedioate* (cf. XVII) (Found: C, 32·6; H, 4·7; Ag, 44·6. $C_{12}H_{20}O_4Ag_2$ requires C, 32·5; H, 4·5; Ag, 48·6%).

Iso-oxoaristic Acid (XVIII).—Aristolactone (460 mg.) in methanol (20 ml.) was treated with cold potassium hydroxide solution (0·5N; 5 ml.) in methanol (90%), the rapidly increasing rotation being observed. On complete conversion into methyl oxoaristate (maximum optical rotation [1]), a further 5 ml. of methanolic potassium hydroxide was added and the solution refluxed for 4 hr. Concentration, acidification, and extraction with ether gave *iso-oxoaristic acid*, as colourless plates (44 mg. from light petroleum), m. p. 143—144° (block), $[\alpha]_D^{20}$ −3·45° (*c* 0·87), $\lambda_{max.}$ 243 mμ (ε 6780) (Found: C, 72·0; H, 8·9. $C_{15}H_{22}O_3$ requires C, 71·8; H, 9·2%).

Dihydroiso-oxoaristic Acid (XIX).—Methyl dihydro-oxoaristate (220 mg.) was refluxed in 0·1N-methanolic potassium hydroxide (25 ml.) for 4 hr. Concentration of the solution, acidification, and extraction with ether gave an oily acidic product (160 mg.), presumed to be dihydroiso-oxoaristic acid, $\lambda_{max.}$ 245 mμ (ε 6300), $[\alpha]_D^{20}$ 0·00°, n_D^{23} 1·5025.

6,7-*Dihydroxyaristolactone*.—Aristolactone (540 mg.) in ice-cold acetone (50 ml.) was treated with potassium permanganate (0·9 g.) in portions during 75 min. The brown precipitate was removed, and the filtrate decolorised with a trace of aristolactone and evaporated to yield a semicrystalline residue (48 mg.). Extraction of the precipitate with hot water, and extraction of the cooled solution with ether, gave further crude material (167 mg.). The product, recrystallised from aqueous ethanol, gave colourless needles of 6,7-*dihydroxyaristolactone*, m. p. 158·5—160°, $[\alpha]_D^{17}$ +128° (*c* 0·39), end-absorption ε 3200 at 210 mμ (Found: C, 68·0; H, 8·55%; Equiv., 272. $C_{15}H_{22}O_4$ requires C, 67·7; H, 8·3%; Equiv., 266).

The aqueous residue remaining after the above extraction with ether was acidified, and the liberated acids were extracted with ether to yield a viscous yellow oil (321 mg.), which gave a red colour with sodium nitroprusside (methyl ketone) but only traces of a flocculent precipitate with 2,4-dinitrophenylhydrazine. The sodium salt of the acid failed to yield a crystalline *S*-benzylthiuronium salt. Oxidation with alkaline potassium permanganate solution, and extraction of the acidic product with ether, gave a semi-crystalline oil, containing succinic acid, identified by partition chromatography on paper with formic acid–phenol–water (1 : 80 : 20) (R_F 0·71).

Periodate Oxidation of 6,7-*Dihydroxyaristolactone*.—Dihydroxyaristolactone (31·3 mg.) was suspended in water (2 ml.), and treated with aqueous N-sodium hydrogen carbonate (1·5 ml.) and 7% aqueous sodium metaperiodate (2 ml.). Dissolution of the lactone was complete in 10 min., but reaction was allowed to proceed for 1½ hr., during which a white precipitate (inorganic) appeared. The solution was filtered and treated with N-hydrochloric acid (3 ml.), 20% aqueous sodium arsenite (2 ml.), aqueous M-sodium acetate (2 ml.), and saturated aqueous dimedone (20 ml.). No precipitation of formaldehyde–dimedone derivative occurred within 2 hr. Similar treatment of milligram quantities of glucose gave quantitative yields of formaldehyde–dimedone.

Attempted Saponification of 6,7-*Dihydroxyaristolactone*.—Dihydroxyaristolactone (200 mg.) in methanol (5 ml.) was refluxed with 0·5N-methanolic potassium hydroxide (3 ml.) for 3½ hr. Neutralisation and extraction with ether yielded unchanged dihydroxyaristolactone (130 mg.). Acidification of the aqueous liquor, extraction with ether, and chromatography from ether on charcoal (5%)–cellulose gave a further 70 mg. of starting material, m. p. 159°. More prolonged treatment with alkali caused some decomposition.

Attempted Isomerisation of 6,7-*Dihydroxyaristolactone*.—Dihydroxyaristolactone (55 mg.) in ethanol (2 ml.) was warmed with a 10% solution of sulphuric acid in 50% ethanol for 2 min. The solution was cooled, diluted with water (10 ml.), and extracted with ether, giving dihydroxyaristolactone (45 mg., from light petroleum–ether), m. p. 159—160° (block), $[\alpha]_D^{18}$ +127°, ε 3300 at 210 mμ.

Tetrahydro-6,7-*dihydroxyaristolactone*.—Dihydroxyaristolactone (90 mg.) in ethanol (10 ml.) was hydrogenated in presence of platinum oxide (12 mg.). Filtration and concentration of the solution gave colourless needles of *tetrahydro*-6,7-*dihydroxyaristolactone* (60 mg. from light petroleum–ether), m. p. 123—124° (block), $[\alpha]_D^{20}$ +32·2° (*c* 0·36 in chloroform) (Found: C, 66·6; H, 9·5. $C_{15}H_{26}O_4$ requires C, 66·7; H, 9·7%).

Sodium Bismuthate Oxidation of Tetrahydro-6,7-*dihydroxyaristolactone*.—Tetrahydro-6,7-dihydroxyaristolactone (33 mg.) in 1 : 1 aqueous dioxan (6 ml.) was mixed with sodium bismuthate (36 mg., containing 80% of $NaBiO_3$) and 80% phosphoric acid (2 ml.) and shaken for 3 hr. (reaction mixture colourless). The suspension was extracted with ether, and the latter dried, and evaporated to yield a pale yellow oil. The oil gave an amorphous 2,4-dinitrophenylhydrazone, but attempts to recrystallise it caused decomposition.

Dehydrogenation Experiments.—(*a*) Semi-solid residues remaining from the preparation of isohexahydroisoaristolactone were refluxed with 20% palladium–charcoal. The violet liquid was slowly distilled, dissolved in cyclohexane, and extracted with 90% phosphoric acid. The acid solution was diluted with water and the azulene re-extracted into cyclohexane for spectroscopic examination. The visible spectrum showed only broad general absorption with no marked maxima; ultraviolet absorption maxima at 244, 279, 289, 306, 333, and 348 mμ. Susz, Pfau, and Plattner [8] give $\lambda_{max.}$ at 290, 308, 336, and 350 mμ and Sörensen and Hougen [8] give $\lambda_{max.}$ 251, 284, 292, 311, 335, 351 mμ for vetivazulene. In oxygen-free 50% sulphuric acid, the azulene showed maxima at 227, 269, and 374 mμ. Chopard-dit-Jean and Heilbronner [8] give $\lambda_{max.}$ for vetivazulene in 50% sulphuric acid at 228, 272, 374 mμ.

(*b*) Crystalline isohexahydroisoaristolactone (400 mg.), dehydrogenated with 20% palladium–charcoal (200 mg.) at 330° for 6 hr., gave no azulenic material, but extraction of the residual mixture with ether gave a brownish oil (30 mg.) which showed well-defined maxima at 228 and 281 mμ and a low-intensity maximum at 312 mμ.

(*c*) Dehydrogenation of oily material (150 mg.) remaining from the preparation of isoaristolactone also gave a violet azulene, $\lambda_{max.}$ 279, 288, 306, 333, and 348 mμ in cyclohexane, and $\lambda_{max.}$ 226, 268, and 374 mμ in 50% sulphuric acid.

(*d*) Hydrogenation was followed by dehydrogenation for oily material (600 mg.) from the preparation of isoaristolactone at 330°. The distillate in hexane deposited colourless crystals (<1 mg.), m. p. 144—145° (block), $\lambda_{max.}$ at 229, 287, and 318 mμ. The azulene, separated as before, had $\lambda_{max.}$ at 280, 289, 306, 333, and 348 mμ in hexane.

TABLE 2.

No.	Compound	No. of double bonds	Reaction time (min.)	Bromine no. (equiv. double bonds)
1	Lupenyl acetate	1	2, 10, 2	1·07, 1·50, 1·55 *
2	Cholesterol	1	2	1·02, 1·09
3	β-Sitosterol	1	10	1·30
4	α-Angelicalactone	1	2, 10	0·77, 0·90
5	Hederagenin Me ester diacetate	1	2, 10	0·65, 0·90
6	Cycloeucalenyl acetate	—	2, 10, 10 (16 hr.)	0·024, 0·076, 0·250 * (1·110)
7	Dihydroaromadendrene	—	2, 10 (16 hr.)	0·03, 0·06 (0·16)
8	Aristolactone (I)	3	2; 10	2·05, 2·35, 2·54, 2·63 *; 2·58, 2·56 *
9	Isoaristolactone (XIII)	3	2, 10 (16 hr.)	2·03, 2·35 (2·59)
10	6,7-Dihydroxyaristolactone (VIII)	2	2, 10	1·90, 2·25
11	Iso-oxoaristaldehyde (IX)	2	2, 10	1·90, 1·98

* Chloroform as solvent.

Tetrahydroisoaristo-6,12-diol (XXIV).—Isohexahydroisoaristolactone (470 mg.) in sodium-dried ether (40 ml.) was mixed with lithium aluminium hydride (230 mg.), added portionwise during 15 min. at room temperature, and reaction allowed to proceed for a further 90 min. Excess of reagent was destroyed by dropwise addition of hydrochloric acid and water (10 ml.). Extraction with ether gave colourless needles (340 mg.; from light petroleum–ether) of *tetrahydroisoaristo-6,12-diol*, m. p. 106—107° (block), $[\alpha]_D^{20}$ +18·7° (*c* 0·3592 in chloroform) (Found: C, 74·5; H, 12·5. $C_{15}H_{30}O_2$ requires C, 74·35; H, 12·5%). Reaction with benzoyl chloride in pyridine gave the 12-*monobenzoate* as a colourless viscous oil, $[\alpha]_D^{23}$ +1·9° (*c* 2·41 in chloroform) (Found: C, 75·4; H, 10·1. $C_{22}H_{34}O_3$ requires C, 76·2; H, 9·9%).

Determination of Bromine Numbers.—Bromine numbers were determined by the pyridine bromide method for the determination of iodine value of the British Pharmacopoeia 1953, but with modifications of (*a*) sample size (2—10 mg.), (*b*) solvent (carbon tetrachloride or chloroform), and (*c*) reaction time (2 min., 10 min., or 16 hr.). The results are shown in Table 2.

We are indebted to the British Drug Houses Ltd., and to Smith, Kline and French Laboratories, Philadelphia, for gifts of raw materials, and to the Cross Trust for a maintenance award (to J. W. Steele). We thank Dr. F. Fish and Mr. P. F. Nelson of this College, and Dr. C. R. Metcalfe of the Royal Botanic Gardens, Kew, for help in authenticating the samples examined.

THE SCHOOL OF PHARMACY, THE ROYAL COLLEGE OF SCIENCE AND TECHNOLOGY, GLASGOW. [*Received, February 11th,* 1959.]

669. *The Thermal Decomposition of Cæsium Permanganate.*

By P. J. Herley and E. G. Prout.

The thermal decomposition of whole and ground crystals of cæsium permanganate has been investigated in the range 240—285°, and the activation energies for the acceleratory and decay coefficients have been measured. The results are in agreement with the theory proposed for the decomposition of potassium permanganate. The effect of pre-irradiation by ^{60}Co γ-rays is similar to that found for pre-irradiated potassium and silver permanganate.

Both the acceleratory and decay periods of the decomposition of potassium permanganate [1] can be represented by Prout and Tompkins's equation:

$$\log_{10}[p/(p_f - p)] = k_2 t + c \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where p_f is the final pressure. The equation has been derived theoretically on the basis of a branching mechanism for the reaction. In the acceleratory period the surface array of product molecules produces lateral strains which are relieved by cracks along which nuclear formation is favoured. The reaction therefore spreads into the crystal down these crevices and covers the inner surfaces with product molecules. The cracking process is repeated on these surfaces and the reaction proceeds through the solid by a system of branching planes of decomposed material. These ultimately interfere, and after the time of maximum velocity the rate is controlled by the number of unchanged permanganate molecules which are contiguous to product molecules.

With silver permanganate [2] Prout and Tompkins's equation is applicable to the acceleratory period only up to $\alpha \approx 0{\cdot}10$. However, if the branching coefficient varies inversely as time, eqn. (1) is transformed into the modified equation:

$$\log_{10}[p/(p_f - p)] = k \log t + c \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

which describes the complete pressure–time curve.

The purpose was to examine the validity of the application of these equations to the decomposition of cæsium permanganate. As well, a knowledge of the kinetics of decomposition of unirradiated cæsium permanganate was necessary for work on the effects of pre-irradiation on permanganates.

Experimental and Results

Rhombic bipyramidal crystals of cæsium permanganate (0·5 mm. × 0·3 mm.) were obtained by adding the nitrate (B.D.H.; 5 g.) and potassium permanganate ("AnalaR"; 4 g.) to water (60 ml.) at 60° and then cooling to 0°. The crystals were twice recrystallized. Large single crystals could not be prepared and "whole" crystals refers to a mass of ~20 mg. of small crystals. The apparatus was similar to that previously described.[1]

The reproducibility of the pressure–time plots for whole crystals was good. For three consecutive runs at 250° the value of k_1 (eqn. 3) was 8·78, 8·76, 8·75 × 10^{-4}, and k_2 (eqn. 1) was 1·74, 1·75, 1·72 × 10^{-2} in the acceleratory periods. Over the decay period k_2 (eqn. 1) was 2·19, 2·17, 2·20 × 10^{-2}.

The pressure–time plots (Fig. 1) show an initial slow acceleration followed by a rapid increase. The decay stage takes the usual form. With ground crystals the slow acceleration is absent and the plots show only the rapid acceleration and decay (Fig. 2).

The pressure–time plots for whole and ground crystals are unaltered if the reaction is interrupted by sudden cooling and subsequent reheating to the original temperature after 3 hr. Likewise, the addition of end products did not affect the decomposition of whole or ground crystals. Exposure to ultraviolet light or bombardment with cathode rays (applied potential

[1] Prout and Tompkins, *Trans. Faraday Soc.*, 1944, **40**, 488.
[2] Prout and Tompkins, *ibid.*, 1946, **42**, 482.

25 kv; residual oxygen pressure $1{\cdot}5 \times 10^{-3}$ cm.) at room temperature before decomposition had no effect. However, exposure to γ-rays from a ^{60}Co source (dose 3·3 Mrad) caused a pronounced change in the pressure–time plot of whole crystals (Fig. 3). A detailed study of the effects of pre-irradiation is in progress.

The percentage decomposition, in terms of the equation:

$$4CsMnO_4 \longrightarrow 2Cs_2O + 4MnO_2 + 3O_2$$

was 96·2% and 90·4% for whole and ground crystals, respectively. Variations of temperature or mass did not significantly affect these percentages.

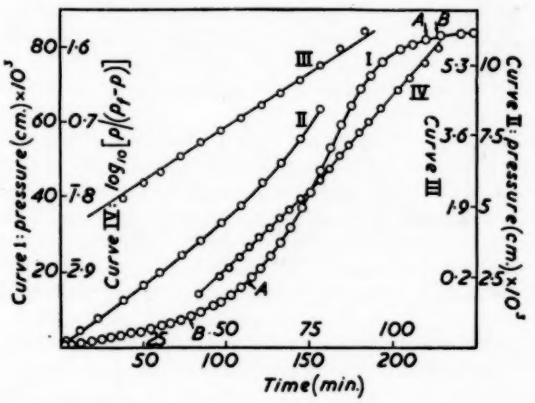


FIG. 1. *Curves* I *and* II: *Pressure–time plots for decomposition of whole crystals of* $CsMnO_4$ *at 250°, and the initial portion of* I *respectively. Curves* III *and* IV: *Plots of* $p^{\frac{1}{2}}$ *against* t, *and Prout and Tompkins's equation, respectively.*

Lower time scale refers to curves I and IV; upper time scale refers to curves II and III.

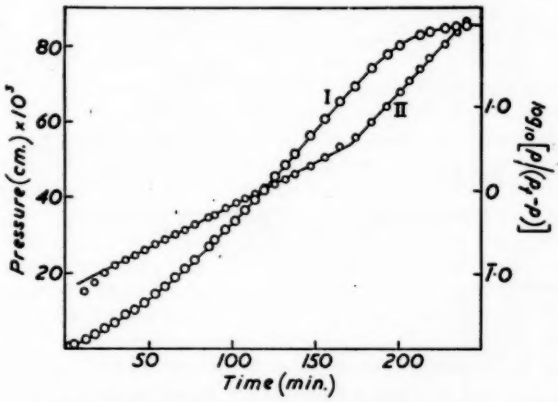


FIG. 2. *Curve* I: *Pressure–time plot for decomposition of ground crystals of* $CsMnO_4$ *at 250°. Curve* II: *Plot for Prout and Tompkins's equation.*

Because of the small size of the crystals it was not possible to follow the decomposition visually, but specimens were removed at various times during the reaction and examined microscopically. It was concluded that no significant fracturing of the crystals occurred from the start of the decomposition until just before the onset of decay. At this point (~150 min. for curve I, Fig. 1) disintegration occurred. The particles were of various sizes but the approximate average was 0·07 mm. × 0·05 mm. No further disintegration took place during the decay period.

The power law

$$p^{1/n} = k_1 t + c \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

applied to whole-crystal decompositions during the slow acceleration, for $n = 2$. The plot of $p^{\frac{1}{2}}$ against t and an enlarged plot of p against t for this period are shown in Fig. 1. For both whole- and ground-crystal decompositions Prout and Tompkins's eqn. (1) was valid for the main acceleratory and decay periods (Figs. 1 and 2, respectively). The extent of applicability

(*AA*) in the case of whole crystals was improved (*BB*) if the origin was transferred to the pressure and time values corresponding to the end of the period of slow acceleration. This point corresponds to the point of departure from linearity of the plot of $p^{\frac{1}{2}}$ against t. This was done for the analyses of all pressure–time curves.

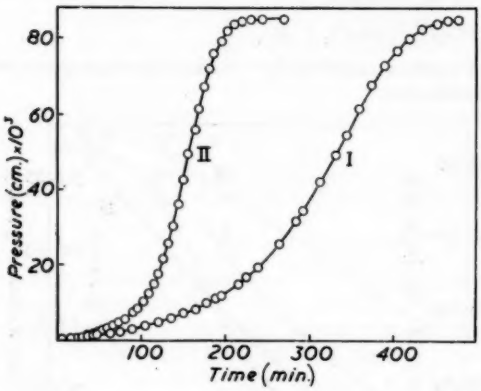


FIG. 3. *Effect of pre-irradiating whole crystals of* $CsMnO_4$ *with* ^{60}Co *γ-rays (dose* 3·3 *Mrad). Curve* I, *unirradiated; and curve* II, *irradiated crystals decomposed at* 240°.

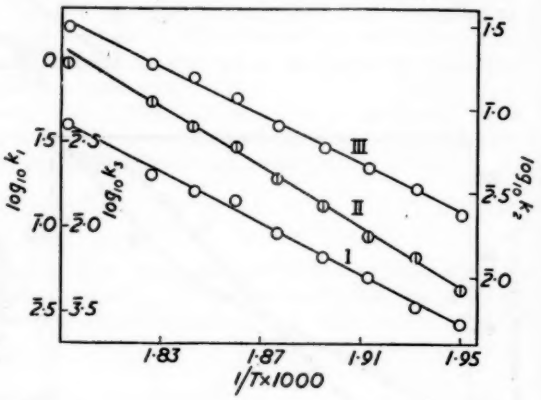


FIG. 4. *Activation energy plots for whole crystals of* $CsMnO_4$. I, *log* k_1; II, *log* k_2; III, *log* k_3; *against* $1/T$ (°K).

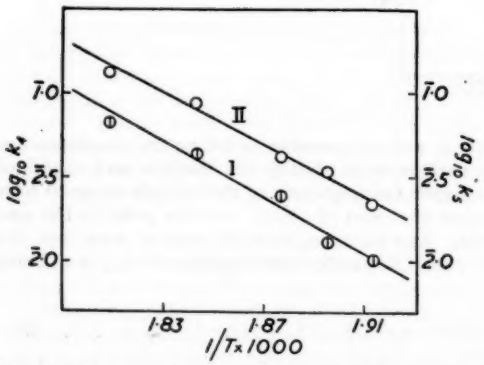


FIG. 5. *Activation energy plots for ground crystals of* $CsMnO_4$. I, *log* k_4; II, *log* k_5; *against* $1/T$ (°K).

The plots of the $\log_{10}$ values of k_1, k_2, k_3, k_4 and k_5 against $1/T$(°K) are well-defined straight lines (Figs. 4 and 5). The activation energies calculated from these plots for whole crystals are 33·7 kcal./mole for the slow acceleration, 40·0 kcal./mole for the rapid acceleration, and

33·6 kcal./mole for the decay. The values for the acceleratory and decay periods for ground crystals are 40·8 kcal./mole and 35·1 kcal./mole, respectively.

Discussion

The decomposition of cæsium permanganate resembles that of potassium and silver permanganate in that, (i) a molecular chain theory involving degenerate branching is improbable, (ii) since irradiation with ultraviolet light and bombardment with cathode rays have no effect on the subsequent decomposition a mechanism of photochemical reduction, as with barium azide, is unlikely, (iii) Prout and Tompkins's theory of branching reaction planes is feasible, and (iv) the thermal decomposition is altered in a similar way by pre-irradiation with 1·3 Mev γ-rays.[3] The kinetics, however, resemble those of potassium permanganate rather than silver permanganate since eqn. (1) describes the characteristics of the pressure–time curves.

The initial slow acceleration of the reaction is of interest. The fit of the square-root plot in this region indicates the growth of two-dimensional nuclei, probably on the crystal surfaces. The negative intercept on the abscissa of the plot of $p^{\frac{1}{2}}$ against t shows that initially the growth of the two-dimensional nuclei is abnormally fast. At the end of the period of slow acceleration, if the crystal faces are covered with a layer of product, strain will be produced in the surface of the reactant. This strain, it is suggested, is relieved by the formation of cracks down which the reaction spreads into the crystal. Thereafter, the reaction proceeds as suggested by Prout and Tompkins.

The non-appearance of the slow acceleration with ground crystals is due to the creation during grinding of a large number of centres from which nuclei grow. These cover the surface very shortly after the commencement of heating. The failure of Prout and Tompkins's equation over a small portion of the curve in the early stages of the decomposition of ground crystals is probably due to the evolution of the gas resulting from this rapid surface coverage.

The improved fit of Prout and Tompkins's equation on transferring the origin is expected, since their mechanism operates after the surface is covered by product.

The difference in the activation energies of the acceleratory and the decay period is possibly associated with the diffusion of the oxygen through the network of cracks formed in the crystal during the main acceleratory period. Reaction during that period comprises the liberation of oxygen at the reactant–product interface and its diffusion through the solid and along the cracks. If the crystal collapses along these cracks just before the onset of the decay stage then during this final stage diffusion along cracks will be absent, since the reaction proceeds by a non-branching mechanism. The measured activation energy will be that for the liberation of oxygen and its diffusion through the solid. It is to be noted that the activation energy over the slow acceleratory period, when the reaction is possibly confined to the growth of two-dimensional nuclei on the external surface, corresponds to the activation energy for the decay period.

Roginsky *et al.*[4] measured the temperature (potassium permanganate, 255°, and cæsium permanganate, 260°) at which the maximum velocity was reached in the same time (120 min.). By using the value 38·6 kcal./mole for whole crystals of potassium permanganate the calculated heat of activation for whole crystals of cæsium permanganate is 39·0 kcal./mole, which is in good agreement with the value found here.

One of us (P. J. H.) thanks the C.S.I.R. (S.A) for a scholarship.

Rhodes University, Grahamstown, South Africa. [*Received, March 20th,* 1959.]

[3] Prout, *J. Inorg. Nuclear Chem.*, 1958, **7**, 368.
[4] Roginsky, Elovich, and Shmuk, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1950, 469.

670. *Nitrosation, Diazotisation, and Deamination. Part VIII.*[1] *The Diazotisation of Weakly Basic Amines in Dilute Perchloric Acid.*

By L. F. Larkworthy.

Diazotisation of *p*-nitroaniline, *o*-nitroaniline, and 2,4-dinitroaniline in dilute perchloric acid is of the first order in amine and in nitrous acid. The reactions are acid-catalysed, but can be studied kinetically with very low reactant concentrations in $<0{\cdot}5$M-acid.

The relative reactivities of amines towards the nitrous acidium ion and dinitrogen trioxide are briefly discussed; and the kinetic results are considered in relation to preparative methods for diazotisation.

Aniline, and amines of similar basicity, are diazotised by dinitrogen trioxide in dilute perchloric acid.[1,2] The reactivities of amines towards dinitrogen trioxide decrease as their basicities are reduced;[1] and, especially with the less basic amines, there is evidence of an acid-catalysed component of the reaction. By choosing suitable reactant concentrations in the diazotisation of *o*-chloroaniline it was possible to show that the acid-catalysed reaction obeyed rate equation (1),[3] and arose from nitrosation by the nitrous acidium ion.[4]

$$\text{Rate} = k_3'\,[\text{Ar}{\cdot}\text{NH}_2][\text{HNO}_2][\text{H}^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The work described in this paper has been carried out to obtain further evidence of the importance of this mechanism, with particular reference to the variation of the reaction rate with the basicities, and hence reactivities, of aromatic amines.

The Diazotisation of p-*Nitroaniline.*—The overall reaction orders (in the perchloric acid concentrations listed in Table 1) have been determined by the half-life method.

Table 1. *Diazotisation of* p-*nitroaniline at* 0°: *overall reaction orders in various concentrations of perchloric acid in excess.*

$[H^+]$	0·00482	0·00964	0·0193	0·0606	0·0998	0·502
Reaction order	1·9	1·9	2·0	2·0	1·9	1·9

Different nitrosation carriers give rise to different rate equations,[5] and the possible second-order rate equations are:

$$\text{Rate} = k_2''[\text{HNO}_2]^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and

$$\text{Rate} = k_2'[\text{Ar}{\cdot}\text{NH}_2][\text{HNO}_2] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Equation (1) reduces to equation (3) when runs are carried out in an excess of perchloric acid. Variation of the initial rate of reaction with reactant concentration has shown that equation (3) is obeyed throughout the range of acidity studied. This has been confirmed by the behaviour of the rate constants calculated from the alternative equations (2) and (3) for runs in which unequal concentrations of reactants were used. Two examples are given in the Experimental section (Table 4). In addition, runs carried out in an excess of amine were of the first order in nitrous acid.

From equations (1) and (3), equation (4) may be derived:

$$k_2' = k_3'[\text{H}^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

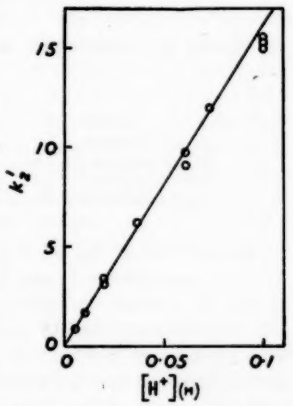
Therefore, if equation (1) is the complete rate equation for the diazotisation of *p*-nitroaniline, k_2' should be proportional to $[H^+]$. The Figure shows that this is true. The

[1] Part VII, preceding paper.
[2] Part II, Hughes, Ingold, and Ridd, *J.*, 1958, 65.
[3] Part IV, *idem*, *J.*, 1958, 77.
[4] Part VI, *idem*, *J.*, 1958, 88.
[5] Part I, Hughes, Ingold, and Ridd, *J.*, 1958, 58.

value of k_3' calculated from the slope of the straight line is 161 sec.$^{-1}$ mole^{-2} l.^{2}. Therefore, throughout the acidity range 0·005—0·5M, *p*-nitroaniline is diazotised according to equation (1).

The Diazotisation of o-*Nitroaniline.*—This amine has been found to diazotise readily in 0·01M-perchloric acid, in which the overall reaction order was 2, and the molecular third-order rate constant was 145 sec.$^{-1}$ mole^{-2} l.^{2}. At pH 5 the order in amine was approximately unity, although the reaction was too slow to give accurate results. Larger concentrations of amine could not be used to increase the rate because the amine was insufficiently soluble. The kinetics of diazotisation seemed similar to those of *p*-nitroaniline, and so a more weakly basic amine was studied.

The Diazotisation of 2,4-*Dinitroaniline.*—Very dilute solutions of this amine could be obtained by prolonged boiling with water, but crystallisation soon occurred: standard solutions could be made up satisfactorily only if the amine was dissolved in 60% perchloric acid and the solution diluted with water until the excess of acid was about 6M. To obtain reasonable rates of reaction without using high concentrations of amine, runs have been carried out in a ten- or twenty-fold excess of nitrous acid. Under these conditions the reaction was found to be of the first order with respect to the amine. Values for the first-order stoicheiometric rate constant are given in Table 2. In runs 16 and 19 the excess of nitrous acid was doubled. This increased the first-order rate constant by a factor of 1·9. Thus, the order in nitrous acid is one, and the rate follows equation (3) under these conditions.



Diazotisation of p-*nitroaniline at* 0°: *plot of molecular second-order rate constants* versus *concentration of hydrogen ions. The value of the rate constant in* 0·5M-*acid* (81·3 *sec.*$^{-1}$ *mole*$^{-1}$ *l.*) *also lies on the line.*

Values for the stoicheiometric second-order rate constants in several concentrations of acid are also given in Table 2. In all these acid concentrations the nitrous acid and the amine ($pK_a = -4·5$; ref. 6) can be considered to be present entirely as their non-ionic forms; the stoicheiometric and molecular rate constants are therefore identical. The third-order

TABLE 2. *Diazotisation of* 2,4-*dinitroaniline at* 0°: *rate constants in several concentrations of perchloric acid.*

Run	[Amine]	$[HNO_2]$	$[H^+]$	k_1' (sec.$^{-1}$)	k_2' (sec.$^{-1}$ mole^{-1} l.)	k_3' (sec.$^{-1}$ mole^{-2} l.^{2})
16	0·000221	0·00469	0·581	0·00153	0·325	5·60
17	0·000221	0·00469	0·313	0·000617	0·132	4·22
18	0·000111	0·00469	0·159	0·000277	0·059	3·71
19	0·000222	0·00235	0·581	0·000818	0·348	5·99

rate constants do not remain constant, but increase with the hydrogen-ion concentration. The reason for this is not yet clear. The complete rate equation is:

$$\text{Rate} = k_3'[\text{Ar}\cdot\text{NH}_2][HNO_2][H^+]^x$$

where x is slightly greater than unity.

DISCUSSION

Mechanism of Reaction.—In Table 3 are collected the third-order molecular rate constants for the amines which have been shown to be diazotised according to a rate of first order in nitrous acid and in amine. Kinetics of this form would be given by both the nitrous acidium ion and the nitrosonium ion when attack of the nitrosation carrier on the free amine is rate-controlling.[5] The nitrosonium ion can be distinguished from the nitrous

acidium ion by the kinetic method described here if its formation can be made rate-controlling: the rate equation would then become independent of the amine and should be equation (2) or of the form:

$$\text{Rate} = k_2'[HNO_2][H^+]$$

according to whether the nitrosonium ion is produced by ionisation of dinitrogen trioxide or by dehydration of the nitrous acidium ion. For the formation of the nitrosonium ion to become rate-controlling it must be removed by the amine as soon as it is formed.

TABLE 3. *Third-order molecular rate constants for the diazotisation of weakly basic amines in dilute perchloric acid.*

Amine	pK_a	k_3' (sec.$^{-1}$ mole^{-2} l.^{2})	[H$^+$] (M)
o-Chloroaniline	2·77	175[5]	0·005—0·02
p-Nitroaniline	0·99[6]	161	0·005—0·5
o-Nitroaniline	−0·29[6]	145	0·01
2,4-Dinitroaniline	−4·5[6]	3·7	0·159

To do this the amine must be reactive and present in large quantities as the free base. At the lowest acidities used, the three nitroanilines were almost entirely present in solution as the free bases. In spite of this the reaction remained fully amine-dependent; and it was therefore impossible to distinguish kinetically between the nitrous acidium and the nitrosonium ion mechanism. From investigations of the catalytic effect of bromide ions on the diazotisation of *o*-chloroaniline, and of the rate of oxygen exchange between nitrous acid and water, it has been deduced that the nitrous acidium ion is responsible for the diazotisation of *o*-chloroaniline;[4] presumably then this is true of the other amines in Table 3. Diazotisation by the nitrosonium ion should become more important as the acidity is increased and the basicity of the amine is reduced; nevertheless, the very slow reaction rate of 2,4-dinitroaniline does not suggest the incursion of a new mechanism of diazotisation.

Reactivities of Amines towards Dinitrogen Trioxide and the Nitrous Acidium Ion.—A notable feature of the results in Table 3 is the small reduction with diminishing basicity of the molecular third-order rate constants for the first three amines. This suggests that the nitrous acidium ion shows little discrimination in its reaction with the more basic amines; it is in marked contrast with the results obtained with dinitrogen trioxide, when, over a comparable decrease in pK_a values, the molecular third-order rate constants were reduced by a factor of 50 (Table 4 of the preceding paper). A full discussion of the relative reactivities of amines towards different nitrosation carriers is deferred until studies being carried out on diazotisation by the nitrosonium ion are complete, but the results clearly imply that a decrease in basicity decreases the reactivities of amines towards dinitrogen trioxide far more than towards the nitrous acidium ion.

Correlation of Kinetic Results with Preparative Methods.—The practical value of a nitrosation carrier depends, not only on its reactivity towards a particular amine, but also on the equilibria governing its concentration. For any amine there is a critical nitrous acid concentration, different for each amine and lower for the more reactive amines, above which diazotisation by dinitrogen trioxide will supersede diazotisation by the nitrous acidium ion. This can be illustrated by reference to *p*-nitroaniline.

This amine is too unreactive to allow direct determination of the third-order molecular rate constant for its reaction with dinitrogen trioxide. However, its σ constant is 1·27,[7] and extrapolation of the results in Table 4 of the preceding paper gives a value of $2{\cdot}5 \times 10^3$ sec.$^{-1}$ mole^{-2} l.^{2} for this rate constant. The molecular third-order rate constant k_3' for its

[6] Paul and Long, *Chem. Rev.*, 1957, **57**, 1.
[7] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, 1940, Chap. VII.

diazotisation by the nitrous acidium ion mechanism is 161 sec.$^{-1}$ mole^{-2} l.^{2}. The contributions to diazotisation by dinitrogen trioxide and the nitrous acidium ion, in 0·01M-perchloric acid with 0·0001M-reactants, can be calculated by substitution in the appropriate terms of equation (5). They are found to be 0·000025[Ar·NH_2] and 0·00016[Ar·NH_2] mole sec.$^{-1}$ respectively. The contribution by the nitrous acidium ion is more than six times

$$\text{Rate} = k_3''[\text{Ar·NH}_2][\text{HNO}_2]^2 + k_3'[\text{Ar·NH}_2][\text{HNO}_2][\text{H}^+] \quad . \quad . \quad . \quad (5)$$
$$= [\text{Ar·NH}_2]\{k_3''[\text{HNO}_2]^2 + k_3'[\text{HNO}_2][\text{H}^+]\}$$

that by dinitrogen trioxide. It can readily be calculated that in concentrations of nitrous acid sufficient to exceed the critical concentration referred to in the previous paragraph, *e.g.*, 0·01M, the dinitrogen trioxide mechanism predominates because of its dependence on the square of the nitrous acid concentration, but in more concentrated perchloric acid, *e.g.*, 0·5M, still with 0·01M-nitrous acid, the nitrous acidium ion mechanism is again more important. The rate of diazotisation by dinitrogen trioxide is decreased in proportion to the fall in the free amine concentration in the more concentrated acid, but in diazotisation by the nitrous acidium ion, the fall in the free amine concentration is more than counterbalanced by the increased standing concentration of the nitrous acidium ion. It is evident that the most efficient way to diazotise *p*-nitroaniline is to use fairly concentrated acid and a high nitrous acid concentration, as is suggested in preparative methods.[8a]

With the more basic amines, *e.g.*, aniline, the free amine concentration is so low that to obtain a reasonable rate of reaction the nitrous acid concentration has to be increased far beyond the critical value. As a result the specifically less reactive dinitrogen trioxide is the most important nitrosation carrier for the diazotisation of the more basic amines in dilute perchloric acid.

Many methods are used in the preparation of diazonium compounds, but, in general, strongly basic amines are diazotised in a slight excess of mineral acid, and weakly basic amines in concentrated acid.[8a] The need for concentrated acid has led to the belief that the amine cation is the reactant:[8b] yet the small quantities of these nitroanilines which dissolve can be diazotised in dilute perchloric acid. The function of the strong acid in large-scale preparative methods is to provide high concentrations of nitrosation carriers more electrophilic than dinitrogen trioxide, and to dissolve reasonable quantities of the amine.

Experimental

The kinetic method was identical with that reported in Part VII and the previous papers. Some examples of the kinetic results are given in Tables 4 and 5.

Table 4. *Diazotisation of* p*-nitroaniline at* 0°*: stoicheiometric second-order rate constants* (*sec.*$^{-1}$ *mole*$^{-1}$ *l.*) *calculated according to alternative rate equations* (2) *and* (3).

Run 10				Run 42			
Stoicheiometric initial concentrations: [Ar·NH_3^+] = 0·0000972M, [HNO_2] = 0·0000324M, [H^+] = 0·1M.				Stoicheiometric initial concentrations: [Ar·NH_3^+] = 0·0000315M, [HNO_2] = 0·0000630M, [H^+] = 0·502M.			
t (min.)	Reaction (%)	k_3'' (eqn. 2)	k_3' (eqn. 3)	*t* (min.)	Reaction (%)	k_3'' (eqn. 2)	k_3' (eqn. 3)
0	14·7	—	—	0	17·5	—	—
2·67	23·5	26·0	7·50	1·40	22·9	62·7	14·3
7·09	38·6	33·8	8·77	3·33	29·3	60·2	14·0
15·1	52·9	32·3	7·67	5·08	34·1	51·3	13·5
22·5	62·8	34·7	7·45	7·33	40·6	57·2	13·9
31·4	72·6	40·5	7·45	10·1	46·2	53·0	13·5
40·8	81·3	52·8	7·93	17·3	58·7	48·5	13·4
52·1	85·1	54·8	7·25	22·6	64·3	44·5	12·7
72·7	92·3	83·3	7·40				

[8] Saunders, " The Aromatic Diazo-compounds," Edward Arnold and Co., London, 1949, (*a*) Chap. I, (*b*) p. 45.

TABLE 5. *Diazotisation of 2,4-dinitroaniline at 0°: examples of first-order rate constants during runs carried out in an excess of nitrous acid.*

Run 16 $[Ar{\cdot}NH_2] = 0{\cdot}000221$M, $[HNO_2] = 0{\cdot}00469$M, $[H^+] = 0{\cdot}581$M.			Run 19 $[Ar{\cdot}NH_2] = 0{\cdot}000222$M, $[HNO_2] = 0{\cdot}00235$M, $[H^+] = 0{\cdot}581$M.		
t (min.)	Reaction (%)	k_1' (sec.$^{-1}$)	t (min.)	Reaction (%)	k_1' (sec.$^{-1}$)
0	25·8	—	0	13·0	—
1·55	35·8	0·00162	1·42	19·0	0·000827
2·80	44·3	0·00171	3·42	27·1	0·000852
5·05	54·0	0·00158	5·74	35·8	0·000880
7·55	62·3	0·00150	11·9	55·0	0·000760
9·65	69·0	0·00151	17·5	66·1	0·000782
12·1	74·5	0·00148	26·2	78·3	0·000805
22·1	86·6	0·00130			
Mean value of $k_1' = 0{\cdot}00153$ sec.$^{-1}$.			Mean value of $k_1' = 0{\cdot}000818$ sec.$^{-1}$.		

The author thanks Professor E. D. Hughes, F.R.S., and Dr. J. H. Ridd for many helpful discussions, and the Department of Scientific and Industrial Research for a Maintenance Award.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER STREET,
LONDON, W.C.1.

[*Received, March 25th*, 1959.]

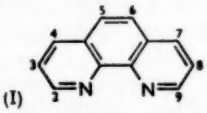
---

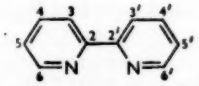
671. *Exchange Studies of Certain Chelate Compounds of the Transitional Metals. Part VII.* Substituent Effects on the Dissociation Rates of Nickel*(II)*–Phenanthroline and –Bipyridyl Complexes.*

By PETER ELLIS, R. HOGG (in part), and R. G. WILKINS.

From ^{63}Ni exchange experiments, the rates of dissociation of nine different ions of the type $[NiA]^{2+}$ † have been investigated, where A represents various phenanthrolines or bipyridyls substituted in the 2-, 4-, or 5-position in the aromatic nucleus. The results are discussed with particular reference to changes in the pre-exponential and energy of activation values.

THERE have been several studies of the effect of ring substitution in 1,10-phenanthroline (phen) (I) and 2,2′-bipyridyl (bipy) (II) in modifying the properties of transition-metal complexes with these ligands. These include spectral,[1,2] redox,[1,3] and thermodynamic stability [4,5] characteristics, but, so far, no systematic investigation of substituent effects on reaction rates has been reported.


(I)


(II)

It is apparent from our earlier work [6] that we might examine for this purpose the rate of exchange of nickel-63 between Ni^{2+} and the monocomplex $[NiA]^{2+}$ † where A represents the phenanthroline or bipyridyl derivative. There are several reasons for this choice. First, of all the elements in the first transition period, probably only nickel gives monocomplexes which exhibit easily measurable dissociation rates, with the *whole* range of

* Part VI, *J.*, 1959, 299.
† Probable co-ordinated water will be ignored in this paper.

[1] Brandt and Smith, *Analyt. Chem.*, 1949, **21**, 1313.
[2] Williams, *J.*, 1955, 137.
[3] Tomkinson and Williams, *J.*, 1958, 2010.
[4] Brandt and Gullstrom, *J. Amer. Chem. Soc.*, 1952, **74**, 3532.
[5] Irving, Cabell, and Mellor, *J.*, 1953, 3417.
[6] Wilkins and Williams, *J.*, 1957, 4514.

ligands studied. Secondly, there is no apparent difficulty in obtaining the mono- as the *predominant* complex species *in solution* even with the sterically hindered ligands, and this might not be the situation with the higher complexes (cf. ref. 5). In addition, with unsymmetrical ligands there is no complication with the formation of *cis*- and *trans*-isomers, as is the case, for example, with the tris-derivative,[7] $[Ni(5\text{-methylphen})_3]^{2+}$. Finally, interpretation of the exchange data is straightforward and these measure the rate constant for overall dissociation.[8] We have accordingly investigated, at different temperatures, the exchange rates of nine different nickel complexes containing ligands substituted in various positions in the aromatic nucleus.

Experimental

Materials.—Radiochemically pure $^{63}Ni(NO_3)_2$ was obtained as described previously.[6] Bipyridyl and phenanthroline were of "AnalaR" quality. 4,4′-Dimethylbipyridyl and 5-methyl-, 5-chloro-, and 4,7-dimethyl-phenanthroline were purchased from G. Frederick Smith Chemical Co., U.S.A., and 5-nitrophenanthroline from L. Light and Co., Ltd. 2-Methylphenanthroline dihydrate and 2-chlorophenanthroline were prepared by recognised methods.[5,9] The materials were either recrystallised from the appropriate solvent (*e.g.*, with 5-chloro- and 5-nitro-phenanthroline when the commercial product was strongly coloured) or it was checked that the original material gave the same kinetic result as a recrystallised portion. This was necessary since some earlier work with 5-methylphenanthroline gave obviously spurious results. The m. p. in the literature and/or the correct analysis was found for each ligand. The following complex compounds were prepared:

$[Ni\ bipy(H_2O)_4](NO_3)_2$.—Bipyridyl (1 mmole) and nickel nitrate (5 mmoles) were heated in aqueous solution. A pale blue material separated when the concentrated solution was cooled, and it was washed with a *small* amount of ice-cold water (Found: C, 30·0; H, 3·8; Ni, 14·3. $C_{10}H_{16}O_{10}N_4Ni$ requires C, 29·2; H, 3·9; Ni 14·3%). The *complex* labelled with ^{63}Ni was prepared similarly.

$[Ni(5\text{-Mephen})Cl_2]$.—5-Methylphenanthroline (1 mmole) and nickel chloride (6 mmoles) were evaporated in aqueous solution to crystallisation. The yellow-green *complex* was dried (P_2O_5) at 80° *in vacuo* for 12 hr. (Found: C, 47·6; H, 3·4; N, 8·8. $C_{13}H_{10}N_2Cl_2Ni$ requires C, 47·9; H, 3·1; N, 8·7%).

Exchange Runs.—The procedure used was very much as described previously for the $[Ni\ phen]^{2+}$–Ni^{2+} exchanges.[6] Chemical and thermal equilibrium were established with the ligand dissolved in nickel nitrate solution (metal/complex $\simeq$ 5/1), and exchange was initiated by the addition of a small amount of ^{63}Ni nitrate. For the separation from nickel ion, the complex was precipitated with naphthalene-1,5-disulphonate ion except with the bipyridyl and phenanthroline complexes for which thiocyanate was used. With the 2-methyl and the 2-chloro-derivative vigorous scratching was necessary for precipitation. The washed solid was decomposed with hot concentrated aqueous ammonia, and radioassayed as nickel dimethylglyoxime.[6] In some cases it was better to preheat the mixture with perchloric acid for about an hour to decompose the separated complex before precipitation with dimethylglyoxime. For runs between 0° and room temperature, the thermostat was placed in a refrigerated room.

The results are shown in Table 1. Several of the runs represent the mean of duplicate experiments. The previous investigation of the phenanthroline system indicated that $R_{(exch)} = k_{(exch)}[mono]$ with the rate independent of acidity in the pH range studied. This behaviour was assumed also for the ligands examined here and, indeed, indicated in several experiments (runs 2—5, 22, and 23). Unless otherwise stated, the pH was 4·8—5·5 and a nitrate medium was used, with no attempt made to maintain a constant ionic strength because of the unimportance of this on the rate. The existence of the mono-species as the predominant complex ion, with excess of nickel ion present, was demonstrated with the bipyridyl compound, since apart from the 2-substituted phenanthrolines, this nickel complex is likely to be the least stable of the series. A small quantity of $^{63}Ni^{2+}$ was added to an equilibrated mixture prepared from nickel ion (193 mmolar) and bipyridyl (35·2 mmolar). A deficiency of dimethylglyoxime was added (*a*) just after mixing, and (*b*) at isotopic equilibrium, and the specific activities of the

[7] Basolo, personal communication.
[8] Wilkins and Williams, *J. Inorg. Nuclear Chem.*, 1958, **6**, 52.
[9] Halcrow and Kermack, *J.*, 1946, 155.

TABLE 1. *Exchange of* $[NiA]^{2+}$ *with* Ni^{2+}.

Run no.	Temp.	[mono] (mmole l.$^{-1}$)	[Ni^{2+}] (mmole l.$^{-1}$)	$t_{\frac{1}{2}}$ (min.)	10^5R (min.$^{-1}$ mole l.$^{-1}$)	$10^3k_{(exch)}$ (min.$^{-1}$)
			A = Bipyridyl			
1	13·8°	35·2	159·6	840	2·4	0·68
2[a]	25·0	35·2	159·6	174	11·5	3·3
3[b]	25·0	35·2	159·6	168	11·9	3·4
4[c]	25·0	33·9	334·5	198	10·8	3·2
5[a]	25·0	70·5	180·6	168	20·9	3·0
6[d]	25·0	35·2	159·6	171	11·7	3·3
7	30·0	35·2	159·6	84	23·8	6·8
8	30·0	35·2	159·6	90	22·2	6·3
9	35·0	35·2	159·6	46·5	43·0	12·2
10	35·0	35·2	159·6	46	43·5	12·4
			A = 4,4′-Dimethylbipyridyl			
11	24·9	39·4	155·8	500	4·4	1·1
12	40·0	39·4	155·8	70	31·1	7·9
			A = Phenanthroline			
13	25·0	3·6	15·9	910	0·22	0·62
14	25·0	3·6	15·9	910	0·22	0·62
15	30·2	3·6	15·9	402	0·51	1·4
16	40·0	3·6	15·9	134	1·52	4·2
			A = 5-Methylphenanthroline			
17	25·0	34·8	160·3	1305	1·5	0·44
18	34·8	34·7	160·3	345	5·7	1·65
19	40·0	34·8	160·3	180	11·0	3·2
20[c]	45·0	36·8	193·2	95	22·5	6·1
21	45·0	34·7	160·3	97	20·4	5·9
22[a]	45·0	34·5	159·0	90	21·8	6·3
23[c]	45·0	34·7	160·3	92	21·5	6·2
24	49·8	34·7	160·3	58	34·1	9·8
			A = 5-Nitrophenanthroline			
25	0·0	42·7	152·9	5790	0·4	0·09
26	20·1	42·7	152·9	295	7·8	1·8
27	30·2	42·7	152·9	79	29·3	6·9
28	30·2	42·7	152·9	76	30·5	7·1
			A = 5-Chlorophenanthroline			
29	25·0	17·5	79·7	378	2·6	1·5
30	25·1	17·5	79·7	380	2·6	1·5
31	34·9	17·5	79·7	105	9·5	5·4
32	39·9	17·5	79·7	54	18·4	10·5
			A = 4,7-Dimethylphenanthroline			
33[f]	39·9	19·7	79·5	618	1·8	0·9
34[f]	40·0	19·6	79·6	648	1·7	0·85
35[f]	59·5	19·6	79·6	60	18·2	9·3
36	59·5	19·6	79·6	54	20·2	10·3
37	59·5	15·8	64·0	55	15·8	10·0
			A = 2-Methylphenanthroline			
38	0·1	63·5	291·0	438	8·25	1·3
39	7·8	52·0	238·0	145	20·4	3·9
40	15·8	52·0	238·0	58·0	51·0	9·8
41	25·0	63·5	466·0	20·5	189	29·8
42	25·0	63·5	291·0	20	181	28·4
			A = 2-Chlorophenanthroline			
43	0·1	68·0	287·0	12	318	46·7
44	0·1	68·0	287·0	12	318	46·7
45	5·2	68·0	287·0	6·5	586	86·2
46	5·2	68·0	287·0	7	544	80·1

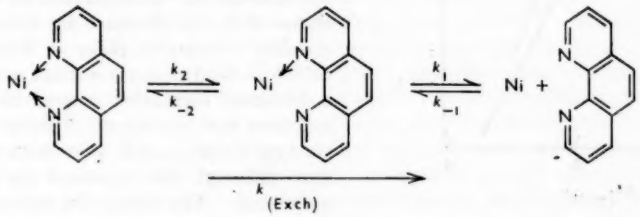
[a] pH = 6·2. [b] pH = 4·2. [c] pH = 3·8. [d] Exchange followed by decrease in specific activity of complex by using $[^{63}Ni\ bipy(H_2O)_4](NO_3)_2$. [e] Solid Ni(5-Mephen)$Cl_2$ added to Ni^{2+}. [f] Chloride medium, since complex nitrate is precipitated below 50°.

precipitated nickel dimethylglyoxime (*a*) and (*b*) determined. The values, (*a*) 682, (*b*) 565 counts/min., showed the predominance of the mono-species [theor. (*b*) 558] and the virtual absence of the bis-species [theor. (*b*) 620]. Further evidence is indicated by the independence of the rate constant of nickel-ion concentration (runs 3 and 4) and by the spectra of the mixture which (against a nickel ion blank) corresponds closely to that of [Ni bipy$(H_2O)_4$]$(NO_3)_2$ in solution with maxima at 610 and 960—970 mμ. With the 2-substituted phenanthrolines, the spectra of the exchange mixtures measured against free nickel ion of the appropriate concentration as " blank " indicated the predominance of the mono-complex with a characteristic peak at 625—635 mμ and ε_M value ~3·5. The spectra and exchange rate (runs 41 and 42) remained unchanged by further addition of nickel. This could be predicted, at least for the 2-methylphenanthroline case, from the estimated dissociation constant for the mono-complex, which would be expected to be smaller than for the bis-complex, and to lie between about 2×10^{-9} ([Ni phen]$^{2+}$) [10] and 6×10^{-5} ([Fe(2-Mephen)]$^{2+}$)[5] since nickel(II) forms a stronger complex with phenanthroline than does iron(II).[10a] The estimated constant of the nickel mono-complex with 2,9-dimethylphenanthroline is 4×10^{-2}.[11]

Earlier results for the phenanthroline compound [6] have been modified. It was apparent from the present study that the energy of activation value of 26·2 kcal. mole^{-1} and the PZ value of 10^{16} obtained previously were too high. The values depended greatly on one determination at 25·0° and a duplicate at this temperature showed this result to be in error. In fact the revised value ($0{\cdot}62 \times 10^{-3}$ min.$^{-1}$) accords well with that obtained indirectly in the previous study ($0{\cdot}60 \times 10^{-3}$ min.$^{-1}$) in [Ni phen$_3$]$^{2+}$–[Ni phen]$^{2+}$–Ni^{2+} exchanges. The present values for E and PZ are obtained from the rate constants shown in Table 1, in addition to the value at 45·1° ($8{\cdot}4 \times 10^{-3}$ min.$^{-1}$) obtained previously [6] as a mean of five separate runs.

Discussion

The results are collected in Table 2. The estimated errors in the E and $\log_{10}PZ$ terms are about ±0·3 unit except for the 2-substituted phenanthrolines where the errors are greater, because of the faster rates. The kinetic parameters refer to the overall dissociation process (rate constant $k_{(exch)}$): *



It has been suggested [13] that, because of the geometry of the rigid phenanthroline molecule, the intermediate step involving " one-ended " attachment will not be important, and applied to our case, $k_{(exch)} = k_2$. Margerum, Bystroff, and Banks [10] have, however, studied the dissociation of [Ni phen]$^{2+}$ at different acidities and explained their results in terms of intermediate species. At low acidity, $k_{(exch)}$ will equal $k_2k_1/(k_1 + k_{-2})$,[13] and our rate constant is thus a composite one. Even in the latter eventuality, it is reasonable to suppose that structural changes which affect k_2 will be reflected in parallel changes in $k_{(exch)}$. One indication that this view is correct insofar as activation energies are concerned is shown by a consideration of the compounds [M bipy$_3$]$^{2+}$ (M = Ni or Fe). With these, where such a mechanism as pictured above can operate (cf. ref. 13), the activation energies

* In this scheme, charge and co-ordinated water will be ignored.

[10] (*a*) Margerum, Bystroff, and Banks, *J. Amer. Chem. Soc.*, 1956, **78**, 4211; (*b*) Anderegg, *Helv. Chim. Acta*, 1959, **42**, 344.

[11] Sone and Kato, *Naturwiss.*, 1958, **45**, 10.

[12] Yasada, Sone, and Yamasaki, *J. Phys. Chem.*, 1956, **60**, 1667.

[13] Basolo, Hayes, and Neumann, *J. Amer. Chem. Soc.*, 1954, **76**, 3807.

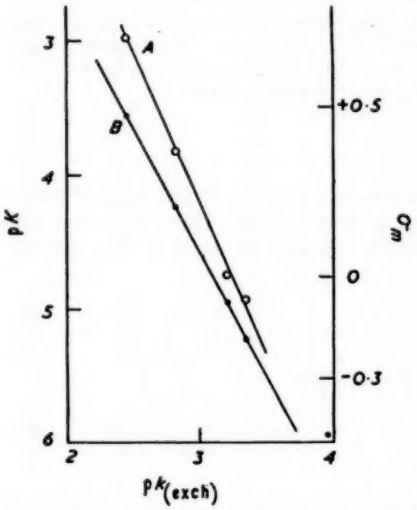
TABLE 2. *Rates of dissociation of* $[NiA(H_2O)_4]^{2+}$ *from* $^{63}Ni^{2+}$ *exchange studies.*

Species A	$10^3 k_{(exch)}$ (min.$^{-1}$; 25°)	pK	E (kcal./mole)	$\log_{10} PZ$ (min.$^{-1}$)
2,2′-Bipyridyl	3·2	4·44 [b]	23·7	15·0
4,4′-Dimethylbipyridyl	1·1	5·32 [b]	24·0	14·7
1,10-Phenanthroline	0·6	4·96 [a]	24·5	14·8
5-Methylphenanthroline	0·45	5·23 [a]	24·4	14·6
5-Nitrophenanthroline	3·55	3·57 [a]	23·5	14·9
5-Chlorophenanthroline	1·5	4·26 [a]	23·9	14·9
4,7-Dimethylphenanthroline	0·11	5·94 [b]	25·7	14·9
2-Methylphenanthroline	29·0	5·42 [b]	20·1	13·2
2-Chlorophenanthroline	~700	—	17·0	12·3

[a] See ref. 4. [b] See ref. 12.

of the dissociation process in strong acid (regarded as measuring k_2) are 27·4 (Fe) [13] and 21·8 (Ni),[14] while the values from [^{14}C]bipyridyl exchanges [15] in *neutral* solution are 28 (Fe) and 22·2 (Ni) kcal. mole^{-1}.

5-Substitution.—Here we are concerned with substituents well removed from the reaction site. The effect of substitution parallels closely the observed behaviour of ring substitution on aromatic reactivity. Compared with the parent compound, the methyl group has an opposite (and smaller) effect than the chloro- or the nitro-group. There is an excellent linear relation between $pk_{(exch)}$ and the pK of the base for this admittedly limited series (see Figure, Curve *B*). Brandt and Gullstrom [4] have measured the thermodynamic stability of the ferroin-type compounds $[FeA_3]^{2+}$ where A are various 5-substituted phenanthrolines, by direct methods, and also from the ratio of formation and dissociation rate constants. Examination of their results shows that the decrease in thermodynamic stability observed, phen ~ 5-phenyl > 5-chloro > 5-nitro, is a result of a *combination* of a decreased formation and an increased dissociation rate constant. A linear relation of our type for $pk_{(diss)}$–pK holds with their results also, although the slopes of the lines differ somewhat. The change in rate observed in the present work results mainly from changes in activation energy, small variations in the entropy factors being scattered in a non-systematic fashion. Substitution of small groups in the large phenanthroline molecule away from the reaction site might be expected only to have an electronic effect without influence on the entropy factor, leaving the form of the transition state unchanged and simply weakening or strengthening the metal–nitrogen bond. With the helpful, although not essential, situation of constant PZ,[16,17] one can attempt a quantitative correlation of the Hammett type [16] of dissociation rates and substituents. There are two difficulties. The 5-substituent effect may be transmitted to the reaction site by two paths and it is therefore difficult to decide whether such substitution is equivalent to *meta* or *para*. Secondly, it is uncertain which σ-type [16,18] should be used for such a reaction as studied



Dependence of $pk_{(exch.)}$ *on* pK *(curve B) and* σm *(curve A).*

[14] Basolo, Hayes, and Neamann, *J. Amer. Chem. Soc.*, 1953, **75**, 5102.
[15] Ellis and Wilkins, unpublished observations.
[16] Jaffe, *Chem. Rev.*, 1953, **53**, 191.
[17] Leffler, *J. Org. Chem.*, 1955, **20**, 1202.
[18] Okamoto and Brown, *ibid.*, 1957, **22**, 493.

here. Notwithstanding this, it is found that a good linear plot of σ_m against $pk_{(exch)}$ is obtained (Figure, Curve *A*) with ρ positive, the reaction being facilitated by low electron density at the reaction site. It does appear then that the substituent effects on free-energy differences, which are predictable for so many organic reactions, apply also to reactivity of metal complexes.

4-*Substitution*.—We only examined one substituted bipyridyl, 4,4'-dimethylbipyridyl, and observed a marked decrease in rate compared with the parent compound. Even when allowance is made for the presence of two methyl groups, the rate for the 4,7-dimethylphenanthroline compound is slower than that for the 5-derivative. This accords with the known higher sensitivity (compared with the 5-compound) of this position to methyl substitution with regard to stability,[12] redox,[1,3] and spectral [1] effects, as well as to relative charge distribution in the phenanthroline molecule from quantum-mechanical calculations.[19] It should be noted, however, that the data for this compound (bottom, right) are removed from the linear plot of the Figure, so that the relation displayed by the 5-substituted series is a very limited one. All three compounds have *PZ* values similar to those in the 5-substituted series.

2-*Substitution*.—We were interested in 2-substituted derivatives because it is known that 2-chloro- and 2-methyl-substitution in phenanthroline markedly modify the properties of its iron(II) complexes. The strong absorption, characteristic of the diamagnetic ferroin type of complex, is absent,[2,5] and $[Fe(2\text{-Mephen})_3]^{2+}$ is paramagnetic.[20] Indeed the $[Fe(2\text{-Mephen})_3]^{2+/3+}$ couple is the only case of an iron phenanthroline couple with a redox potential less positive than that of the $Fe^{2+/3+}$ aquo system.[3]

The effect of 2-substitution on the dissociation rates is drastic. The $[Ni(2\text{-Mephen})]^{2+}$ ion dissociates almost 50 times and the $[Ni(2\text{-Clphen})]^{2+}$ ion over 1000 times faster than the unsubstituted compound at the same temperature. The rates are just measurable with the chloro-compound and since the separation procedure is not rapid it must be emphasised that the kinetic data, and more especially the Arrhenius parameters, are less accurate than with the other ligands. The increased rates are produced by a decrease of the activation energy, partly offset by a lower frequency factor. This type of "compensating" behaviour has been well recognised for some time.[17,21] The consequence in this case is that the 2-chlorophenanthroline compound has (for this type of ligand) the remarkably low activation energy of 17 kcal. mole^{-1}. The substituents, being now adjacent to the co-ordinating nitrogen, are in a position to alter the relative shapes of the reactants and the transition state, and probably, in particular, the vibrational, rotational, or translational energy levels, thus producing entropy changes and concomitant potential-energy differences also, the latter reflected in activation energy changes. The steric interaction between the 2-substituent and the reaction centre must be less in the transition state than in the reactant state although it is not immediately obvious why the chlorine should have such a larger effect than the sterically similar methyl group. However, we must remember that superimposed on this steric effect will be the usual electronic one, and it might very well be that the chloro-group will have a relatively much larger rate-accelerating effect than is the case with the 5-substituents, since the 2-position is a sensitive one, judging from π-electron distribution calculations.[19]

We are grateful to the University of Sheffield for Maintenance Scholarships (to P. E. and R. H.).

THE UNIVERSITY, SHEFFIELD. [*Received, April 2nd*, 1959.]

[19] Longuet-Higgins and Coulson, *J.*, 1949, 971.
[20] Irving, quoted in ref. 3.
[21] For recent discussion and previous literature see Blackadder and Hinshelwood, *J.*, 1958, 2728.

672. *Reaction of Periodate with Compounds containing Active Methylene Groups.*

By J. L. Bose, A. B. Foster, and R. W. Stephens.

The action of periodate on chloro-, bromo-, and iodo-acetaldehyde has been examined. A convenient source of the halogenoacetaldehydes is by reaction of periodate with the 1,4-dideoxy-1,4-dihalogeno-derivatives of DL-threitol, and synthesis of the latter compounds from *cis*-but-2-ene-1,4-diol is described. A mechanism for the hydroxylation of active methylene groups by periodate is suggested and some supporting evidence is provided.

In addition to cleaving 1,2-diols and related compounds periodate can also cause other reactions.[1-3] Thus, the observation [4] that, in the presence of excess of periodate, malonic acid consumed 3 mol. of oxidant and gave 2 mol. of carbon dioxide led to the suggestion [4] that periodate could hydroxylate active methylene groups, thereby permitting further glycol cleavage. Although numerous reactions in this class have been reported,[4-6] little appears to be known of the mechanism. In seeking further experimental data we investigated the action of periodate on the monohalogenoacetaldehydes.

Although numerous methods are available for the synthesis of chloro-[7] and bromo-acetaldehyde [8] the iodo-analogue [9] is less accessible. A new and convenient method for the preparation of all three compounds was developed in the present work. The halogeno-acetaldehyde was generated in the reaction solution by treating the appropriate 1,4-di-halogeno-derivative of DL-butane-2,3-diol (1,4-dideoxy-1,4-dihalogeno-DL-threitol) with periodate. Hatch and Alexander [10] recorded a preparation of chloroacetaldehyde by treatment of 3-chloropropane-1,2-diol with periodate. The dihalogeno-compounds rapidly consumed 1 mol. of oxidant with the release of 2 mol. of the halogenoacetaldehyde. After equimolar amounts of periodate and dihalogeno-compound had reacted, the halogeno-acetaldehyde formed could be isolated and characterised as its 2,4-dinitrophenylhydrazone. By using an excess of periodate, the reaction of the halogenoacetaldehyde with the oxidant could be studied. A particular value of the method is that the 1,4-dihalogeno-DL-butane-2,3-diols, which are stable crystalline compounds, may be conveniently stored as precursors of the halogenoacetaldehydes. The 1,4-dihalogeno-compounds may be obtained by the following route. Commercial but-2-ene-1,4-diol was shown to be predominantly *cis* when acidic hydrolysis of the crystalline epoxide obtained on treatment with perbenzoic acid yielded DL-threitol characterised as a di-*O*-benzylidene derivative; the epoxide was therefore 2,3-anhydroerythritol. Addition of bromine to *cis*-but-2-ene-1,4-diol readily yielded

[1] Bobbitt, *Adv. Carbohydrate Chem.*, 1956, **11**, 1.
[2] Greville and Northcote, *J.*, 1952, 1945.
[3] Foster, Stacey, and Stephens, *J.*, 1959, 2681.
[4] Huebner, Ames, and Bubl, *J. Amer. Chem. Soc.*, 1946, **68**, 1621; Sprinson and Chargaff, *J. Biol. Chem.*, 1946, **164**, 433.
[5] Schwarz and MacDougall, *J.*, 1956, 3065.
[6] Wolfrom and Bobbitt, *J. Amer. Chem. Soc.*, 1956, **78**, 2489 and references cited therein.
[7] Fritsch and Schumacher, *Annalen*, 1894, **279**, 301; Glinsky, *Z. angew. Chem.*, 1867, 678; Reisse, *Annalen*, 1890, **257**, 331; Ohta and Imamura, *Reports Govt. Chem. Ind. Res. Inst., Tokyo*, 1953, **48**, 311 (*Chem. Abs.*, 1955, **49**, 15,730); Malinovskiĭ, *J. Gen. Chem.* (*U.S.S.R.*), 1939, **9**, 832 (*Chem. Abs.*, 1940, **34**, 375); Crane, Forrest, Stephenson, and Waters, *J.*, 1946, 827; Guinot and Tabuteau, *Compt. rend.*, 1950, **231**, 234; Shchukina, *Zhur. obshchei Khim.*, 1948, **18**, 1653 (*Chem. Abs.*, 1949, **43**, 2575); Weygand, Eberhardt, Linden, Schäffer, and Eigen, *Angew. Chem.*, 1953, **65**, 525.
[8] Mauguin, *Compt. rend.*, 1908, **147**, 748; *Ann. Chim.* (*France*), 1911, **22**, 364; Fischer and Landsteiner, *Ber.*, 1892, **25**, 2549; Hibbert and Hallonquist, *Canad. J. Res.*, 1931, **5**, 428; Stepanow, Preobrashenski, and Schtschukina, *Ber.*, 1926, **59**, 2533; Yanovskaya and Terent'ev, *Zhur. obshchei Khim.*, 1952, **22**, 1598 (*Chem. Abs.*, 1953, **47**, 9258).
[9] Chautard, *Ann. Chim. Phys.*, 1839, **16**, 145; Glinsky, *Z. angew. Chem.*, 1868, 618.
[10] Hatch and Alexander, *J. Amer. Chem. Soc.*, 1945, **67**, 688.

a *threo*-2,3-dibromide which was converted into 1,2:3,4-dianhydro-DL-threitol (DL-*threo*-1,2:3,4-diepoxybutane) by treatment with sodium hydroxide. When the diepoxide was treated with hydriodic acid in aqueous tetrahydrofuran at −10°, 1,4-dideoxy-1,4-di-iodo-DL-threitol was obtained in high yield. By using the appropriate acid the 1,4-dibromo- and 1,4-dichloro-analogues were also easily prepared in satisfactory yield. The location of the halogen atoms on the terminal positions in these compounds would be expected by analogy with reactions of related compounds; [11] it was proved by their rapid consumption of 1 mol. of periodate with the formation of halogenoacetaldehyde.

Previous work [3] has shown that alkyl iodides react with periodate according to reaction (1). Similar reactions with iodoacetaldehyde [reaction (2) starting from 1,4-dideoxy-1,4-di-iodo-DL-threitol] would require 9 mol. of oxidant with the liberation of 4 mol. acid and 1 mol. of formaldehyde. In the presence of excess of periodate the di-iodo-compound rapidly consumed 1 mol. of oxidant and thereafter uptake of periodate was slow. The time of half-oxidation of iodoacetaldehyde was 140 hr. [*i.e.*, after consumption of 5 mol. oxidant on the assumption that equation (2) operates]. After 2016 hr. 10·66 mol. of oxidant had been consumed; from a plot of the results, the latter part of the curve indicated a very slow oxidation, and extrapolation to zero time gave an uptake of *ca.* 9 mol. of oxidant for the principal reaction pathway. However, formaldehyde could not be detected during the reaction and only 25% of the acidity predicted by reaction (2) developed. Loss of formaldehyde by oxidation is unlikely, since it is known [3] to survive long periods in conditions represented by reaction (4). Formaldehyde would not be an expected product if hydroxylation occurred [reaction (3)] but in this case the required consumption of oxidant (11 mol.) and liberation of acid (6 ml.) are much greater than the observed values.

$$R{\cdot}CH_2I + 3IO_4^- \longrightarrow R{\cdot}CH_2{\cdot}OH + 4IO_3^- + H^+ \quad . . . . . (1)$$

$$[CH(OH){\cdot}CH_2I]_2 \xrightarrow{IO_4^-} 2CHO{\cdot}CH_2I \xrightarrow{6IO_4^-} 2CHO{\cdot}CH_2{\cdot}OH + 2H^+$$
$$\xrightarrow{2IO_4^-} 2H{\cdot}CO_2H + 2H{\cdot}CHO \quad . . . . . (2)$$

$$[CH(OH){\cdot}CH_2I]_2 \xrightarrow{IO_4^-} 2CHO{\cdot}CH_2I \xrightarrow{2IO_4^-} 2[CHO{\cdot}CHI{\cdot}OH]$$
$$\longrightarrow 2CHO{\cdot}CHO + 2HI \xrightarrow{8IO_4^-} 4H{\cdot}CO_2H + 2H^+ + 2IO_3^- \quad . (3)$$

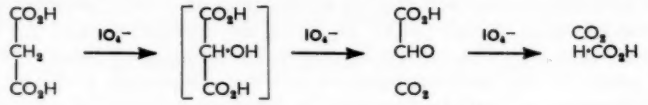
$$R{\cdot}CH(OH){\cdot}CH_2I \xrightarrow{4IO_4^-} R{\cdot}CHO + H{\cdot}CHO + IO_3^- + H^+ \quad . . . . (4)$$

The results obtained with bromo- and chloro-acetaldehyde do not clarify the situation. Thus, after 2016 hr. bromoacetaldehyde had consumed 0·7 mol. of oxidant and liberated 0·43 mol. of acid, and chloroacetaldehyde had consumed 0·59 mol. of oxidant and liberated 0·375 mol. of acid. In view of the extreme slowness of these reactions they were not followed to completion. It may be noted also that, whilst ethyl bromoacetate reacted with periodate with the liberation of bromine, alkyl bromides such as 1,2-dibromoethane and 6-bromo-6-deoxy-1,3:2,4-di-*O*-ethylidene-D-glucitol [3] did not react. Although the precise mechanism of the periodate–halogenoacetaldehyde reaction cannot be deduced from the preceding results, it appears not to involve hydroxylation of the methylene group.

In their detailed study of the reaction with periodate of compounds containing active methylene groups, Huebner, Ames, and Bubl [4] observed that, although a wide range of compounds reacted, there were certain notable exceptions, *e.g.*, diethyl malonate, ethyl acetoacetate and cyanoacetic acid. Acetylacetone was also reported [4] to be resistant to periodate but Wolfrom and Bobbitt [6] found it to be slowly oxidised, as were also 1-phenylbutane-1,3-dione and 1,3-diphenylpropane-1,3-dione.

[11] Foster and Overend, *J.*, 1951, 1132; Wiggins and Wood, *J.*, 1950, 1566.

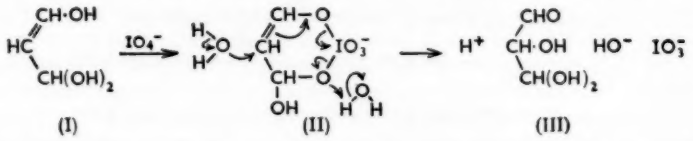
In the presence of excess of periodate, malonic acid was considered [4] to react by the following route:



By comparison of the rate of the overall oxidation with those of tartronic and glyoxylic acid, intermediates in the above sequence, it was inferred that the hydroxylation stage was rate-determining. An initial hydroxylation stage is also strongly indicated in the periodate oxidation of benzyloxymalondialdehyde [5] and cyclohexane-1,3-dione.[6]

From the results of Huebner *et al.*,[4] the influence of R in compounds of the type $R{\cdot}CH_2{\cdot}CO_2H$ in promoting attack by periodate follows the sequence $CO_2H > Ac > CO_2Et > CN \simeq 0$. Relative activating influences have been determined in other ways. Thus by studying the coupling reaction of *p*-nitrobenzenediazonium fluoroborate with compounds containing active methylene groups Hünig and Boes [12] obtained, *inter alia*, the sequence $Ac > CN > CO_2Et > CO_2H$ for the relative activating abilities of the respective groups. From the ionisation constants of acids [13] $R{\cdot}CH_2{\cdot}CO_2H$ the sequence $CN > CO_2H > CO_2Et > Ac$ is obtained, which reflects the ability of these groups to enhance the ionisation of the respective acids. Neither of the last two sequences shows any notable relation to the first, which suggests that a different mechanism operates in each case.

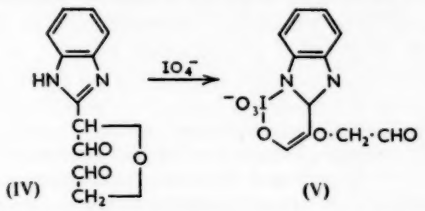
That ethyl acetoacetate, cyanoacetic acid and diethyl malonate are unaffected by periodate whereas acetoacetic acid, ethyl hydrogen malonate, and malonic acid undergo hydroxylation may be explained if this is assumed to require formation of a cyclic intermediate. With malondialdehyde as an example, hydroxylation could result from the breakdown of the six-membered cyclic complex (II) formed between periodate and the hydrated enol form (I) of the dialdehyde, to yield tartronic aldehyde (III) which may react further with periodate by normal glycol cleavage. The reaction sequence (I ⟶ II ⟶



III) involves the IO_4^- ion but it is possible that reaction may proceed through hydrated forms of the ion.[14,15] In general, the presence of an active methylene group will not be the sole factor which determines the occurrence of oxidation. Instead, the structural requirements for complex formation, and hence oxidation, will be the presence on 1,3-carbon atoms of hydroxyl groups, one of which must be provided by enolisation. It will be shown later that reaction will proceed if the non-enolic hydroxyl group is replaced by an amino-group. Thus in the compounds noted which contain an active methylene group but do not react with periodate, enolisation is possible but a cyclic complex cannot be formed. The postulated reaction sequence may be used to explain other observations; thus, the initial product (IV) of the reaction of 2-(1,4-anhydro-D-*xylo*-2,3,4,5-tetrahydroxybutyl)benzimidazole which reacts [4] further with periodate may do so through a complex of the type (V) in which an NH group is involved in complex formation. In a study of the reaction of cyclohexane-1,3-dione with periodate Wolfrom and Bobbitt [6] concluded that the annexed reaction sequence occurred. Whilst the initial stage may be explained in

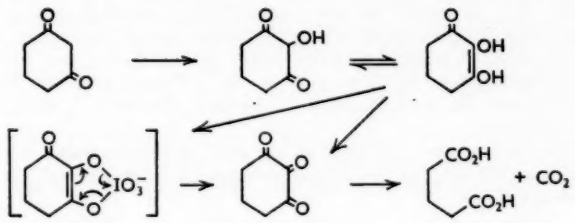
[12] Hünig and Boes, *Annalen*, 1953, **579**, 28.
[13] "Physikalisch-Chemische Tablellen," Springer, Berlin, 1936, Suppl. 3, Vol. III, pp. 2109 *et seq.*
[14] Crouthamel, Hayes, and Martin, *J. Amer. Chem. Soc.*, 1951, **73**, 82.
[15] Buist and Bunton, *J.*, 1954, 1406.

terms of the reaction sequence (I ⟶ II ⟶ III) the second stage may also be explained in terms of the formation and decomposition of an intermediate cyclic complex (VI).



(IV) (V)

The operation of the reaction mechanism as suggested in this paper implies that, for example, 3-hydroxybutyraldehyde (aldol), β-hydroxy- and β-amino-propionic acid ought to be oxidised by periodate. Reaction was in fact observed to occur slowly at pH 4—5 with aldol and at pH 2—2·5 with these acids; formaldehyde was produced from the acids. β-Propionolactone was not attacked by periodate. Failure to recognise these reactions before may have been due to their slowness, coupled with the possibility



(VI)

that reaction of substituted compounds of the type R·CH(OH)·CH(OR')·CHO and R·CH(OH)·CH(OR')·CO_2H, encountered in the periodate oxidation of carbohydrates, may be retarded (cf. Huebner *et al.*[4]) by the presence of OR' and/or by involvement of the hydroxyl and aldehyde groups in internal hemiacetal formation with the appropriate functional groups in R.

The observation [3] that β-iodopropionic acid consumed 5—6 mols. of periodate with the release of formaldehyde and development of acidity may now be explained in terms of an initial reaction as shown in equation (1) followed by reaction of the type (I ⟶ II ⟶ III), yielding glyceric acid which undergoes [4] further glycol cleavage.

Wolfrom and Bobbitt [6] have shown that carbocyclic 1,3-diketones react much more rapidly with periodate than do the corresponding acyclic compounds, which implies that, in terms of the reaction mechanism suggested in this paper, cyclic-complex formation in these cases must be greatly facilitated.

The influence of stereochemical variations on the rate of oxidation of 1,2-diols [1,16] strongly indicates a path involving a 5-membered cyclic intermediate. Isolation of such a complex intact presents a problem since in general it will decompose rapidly to the products of oxidation. By analogy, the formation of a 6-membered cyclic complex from periodate and a 1,3-diol may be reasonably expected since the minimum O–O distances obtainable without deformation of bond angles in, for example, propane-1,2- and -1,3-diol are similar (2·49 and 2·51 Å respectively [17]). A 6-membered cylic complex of a simple 1,3-diol would not be expected to decompose. It is of interest that Barker and Shaw [18] have suggested

[16] Brimacombe, Foster, Stacey, and Whiffen, *Tetrahedron*, 1958, **4**, 351; Wasserman in "Steric Effects in Organic Chemistry," Academic Press, New York, 1956; Schwarz, *J.*, 1957, 276.
[17] Barker, Bourne, and Whiffen, *J.*, 1952, 3865.
[18] Barker and Shaw, *Proc. Chem. Soc.*, 1957, **259**; *J.*, 1959, 584.

that a relatively stable terdentate complex may be formed between periodate and a 1,2,3-triol of suitable stereochemistry.

Buist and Bunton [15] found that when an excess of ethylene glycol was added to aqueous periodic acid at pH 2 or 5 there was an immediate drop in pH followed by slower changes. This would be expected if the periodate complex was a stronger acid than periodic acid itself. We have found that the addition of numerous 1,3-diols to aqueous periodic acid at pH of 1·86, 2·6, or 3·57 caused no detectable change in pH. However, significant pH changes resulted when 1,3-diols were added to aqueous sodium metaperiodate (pH 4—5). Surprisingly perhaps, butane-1,4-diol and *cis*-but-2-ene-1,4-diol also lowered the pH and in fact the latter diol effected the greatest change of all the diols examined and also slowly consumed oxidant. Pentane-1,5-diol and hexane-1,6-diol caused no pH change. It thus seems possible that periodate can form complexes with 1,3-diols.

Experimental

2,3-*Anhydroerythritol*.—To a solution [19] of perbenzoic acid in chloroform (330 ml.) at −5° *cis*-but-2-ene-1,4-diol (11·426 g., b. p. 100—102°/0·6—0·7 mm., n^{20} 1·4790) was added and the mixture stored at −5°. A crystalline precipitate slowly separated during 14 hr. and after 4 days the reaction was complete as shown by determination of unchanged perbenzoic acid.[19] The precipitate was collected, washed with chloroform (3 × 100 ml.), and dried *in vacuo*, yielding **2,3-*anhydroerythritol*** (8·86 g., 66%), m. p. 54·5—56°. Recrystallisation from acetone–ether at −15° afforded hygroscopic crystals, m. p. 57·5—58·5° (Found: C, 46·3; H, 7·7. $C_4H_8O_3$ requires C, 46·2; H, 7·7%).

2,3-Anhydroerythritol reacted slowly, if at all, with bromine water. The consumption of oxidant in a solution (100 ml.) of the anhydro-compound (0·684 mmol.) in 0·0625M-sodium metaperiodate was as follows:

Time (min.)	44	125	356	1276
Consumption of periodiate (mol.)	0·124	0·185	0·215	0·365

Hydrolysis of **2,3-*Anhydroerythritol*.**—A solution of the anhydro-compound (2 g.) in 0·1N-sulphuric acid (8 ml.) was boiled under reflux for 1 hr. and then neutralised with barium carbonate. After removal of insoluble inorganic material the filtrate was evaporated to yield a syrup (2·3 g., 98%) which was dissolved in ethanol and treated with charcoal. DL-Threitol was obtained which, after recrystallisation from ethanol, had m. p. 59—64°; Griner [20] records m. p. 72°.

The product (0·684 mmol.) rapidly consumed 3·02 mol. of 0·0625M-sodium metaperiodate.

The product (0·96 g.), by the methods of Hockett [21] and Lucas and Baumgarten,[22] gave a di-*O*-benzylidene derivative (1·92 g., 81%), m. p. 221—223° after three recrystallisations from benzene (Found: C, 72·6; H, 6·3. Calc. for $C_{18}H_{18}O_4$: C, 72·5; H, 6·0%). Hockett [21] gives m. p. 220—222° for di-*O*-benzylidene-D-threitol; Lucas and Baumgarten [22] give m. p. 221—223° for the L-isomer. Di-*O*-benzylidene-erythritol is reported [22] to have m. p. 201°.

1,2:3,4-*Dianhydro*-DL-*threitol*.—A mixture of *cis*-but-2-ene-1,4-diol (158 ml.) and ether (300 ml.) was shaken whilst bromine was cautiously added (cf. Prevost [23]). The olefin dissolved gradually. After 1 hr. a slight excess of bromine had been added and the mixture was stored overnight at room temperature, then washed with aqueous sodium thiosulphate and water. Evaporation of the dried ($MgSO_4$) ethereal solution yielded a syrup (443 g., 80%), presumably 2,3-dibromo-2,3-dideoxy-DL-threitol.

The dibromo-compound (55 g.) in dry ether (100 ml.) was treated with potassium hydroxide (30 g.) previously powdered under ether (cf. Prevost,[23] Griner,[20] and Przybytek [24]). After

[19] Braun, *Org. Synth.*, Coll. Vol. I, 1932, p. 431.
[20] Griner, *Compt. rend.*, 1893, **117**, 554; cf. Thiele, *Annalen*, 1899, **308**, 341.
[21] Hockett, *J. Amer. Chem. Soc.*, 1935, **57**, 2260.
[22] Lucas and Baumgarten, *ibid.*, 1941, **63**, 1653.
[23] Prevost, *Compt. rend.*, 1926, **183**, 1292.
[24] Przybytek, *Ber.*, 1884, **17**, 1091.

30 min. the mixture was boiled under reflux for a further 30 min., then filtered and concentrated. Distillation of the residue gave 1,2:3,4-dianhydro-DL-threitol (5 g., 26%), b. p. 62°/29 mm., 142°/~760 mm., n^{20} 1·4365; Przybytek [24] gives b. p. 138°/767 mm., n^{20} 1·4400.

Action of Hydrogen Halides on 1,2:3,4-*Dianhydro*-DL-*threitol*.—The following general procedure was adopted.[3,25] The diepoxide (*ca.*, 2 g.) in tetrahydrofuran (100 ml.) at −15° was treated with a slight excess of 56% hydriodic acid, 45·5% hydrobromic acid, or 10N-hydrochloric acid at such a rate that the temperature did not exceed 0°. After storage at −5° for *ca.* 40 hr. solid sodium thiosulphate and potassium carbonate were added to remove free iodine and excess of acid. Sufficient water was then added to form two phases. The organic layer was separated, combined with two ether-extracts of the aqueous layer, dried ($MgSO_4$), and evaporated. The following compounds were thus obtained.

(i) 1,4-*Dideoxy*-1,4-*di-iodo*-DL-*threitol* (79%), m. p. 96—97° after recrystallisation from benzene (Found: C, 14·4; H, 2·2; I, 74·1. $C_4H_8O_2I_2$ requires C, 14·0; H, 2·3; I, 74·4%). Nesmayanov and Lutsenko [26] report m. p. 109° for a 1,4-di-iodobutane-2,3-diol formed by reaction of iodine with the 1,4-bischloromercuributane-2,3-diol (obtained by the treatment of butadiene sequentially with mercuric acetate, potassium chloride, and sodium hydroxide).

The di-iodo-compound (0·51 g.) in dry pyridine (7 ml.) was treated with toluene-*p*-sulphonyl chloride (1·71 g.) in pyridine (3 ml.) for 6 hr. at room temperature. Longer reaction times decreased the yield. The mixture was diluted with sodium hydrogen carbonate solution, then acidified with dilute hydrochloric acid and extracted several times with chloroform. The combined extracts were washed successively with dilute hydrochloric acid and sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated. Recrystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave 1,4-*dideoxy*-1,4-*di-iodo*-2,3-*di*-O-*toluene*-*p*-*sulphonyl*-DL-*threitol* (0·24 g., 25%), m. p. 139—140° (Found: C, 33·0; H, 2·9; I, 39·0; S, 9·85. $C_{18}H_{20}O_6I_2S_2$ requires C, 33·2; H, 3·1; I, 39·1; S, 9·8%).

(ii) 1,4-Dibromo-1,4-dideoxy-DL-threitol (87%), m. p. 79—81° after recrystallisation from benzene (Found: C, 19·2; H, 3·4; Br, 64·4. Calc. for $C_4H_8O_2Br_2$: C, 19·4; H, 3·2; Br, 64·5%). Griner [20] gives m. p. 83° for the compound prepared by hydroxylation of 1,4-dibromobut-2-ene with permanganate.

(iii) 1,4-Dichloro-1,4-dideoxy-DL-threitol (87%), m. p. 72—73° (from benzene) (Found: C, 30·4; H, 5·0; Cl, 44·9. $C_4H_8O_2Cl_2$ requires C, 30·2; H, 5·1; Cl, 44·7%). Schalit [27] gives m. p. 126—126·5° for the *erythro*-compound obtained by the action of fuming hydrochloric acid at 100° on erythritol. Kilmer *et al.*[28] give m. p. 62—63° for the product, presumably the *threo*-compound, obtained by hydroxylation of 1,4-dichlorobut-2-ene with permanganate.

Action of Periodate on the 1,4-*Dideoxy*-1,4-*dihalogeno-derivatives of* DL-*Threitol*.—(*a*) 1,4-Dideoxy-1,4-di-iodo-DL-threitol (0·47 g.) was added to 0·25M-sodium metaperiodate (6 ml.). The iodo-compound, which is sparingly soluble in water, dissolved within 2 min., and after 5 min. the solution was extracted ten times with ether. The combined and dried ($MgSO_4$) extracts were concentrated (removal of all the solvent caused decomposition of the residue) and treated with an excess (*ca.* 200 ml.) of an acidified (HCl) saturated solution of 2,4-dinitrophenylhydrazine in ethanol. There was an immediate precipitate (0·35 g., 37%) of, presumably, *iodoacetaldehyde* 2,4-*dinitrophenylhydrazone*, m. p. 147—148° (from ethanol) (Found: C, 28·7; H, 2·25; N, 16·5. $C_8H_7O_4N_4I$ requires C, 27·4; H, 2·0; N, 16·0%).

By the same procedure 1,4-dibromo-1,4-dideoxy-DL-threitol gave bromoacetaldehyde 2,4-dinitrophenylhydrazone, m. p. 155—156° (from ethanol) (Found: C, 32·0; H, 2·3; N, 18·6. Calc. for $C_8H_7O_4N_4Br$: C, 31·7; H, 2·3; N, 18·5%). Newbold [29] gives m. p. 155—157°; Heilbron *et al.*[30] give m. p. 150°.

Similarly 1,4-dichloro-1,4-dideoxy-DL-threitol gave chloroacetaldehyde 2,4-dinitrophenylhydrazone, m. p. 154—155° (from ethanol) (Found: C, 37·35; H, 3·0; N, 22·0. Calc. for $C_8H_7O_4N_4Cl$: C, 37·1; H, 2·7; N, 21·7%). Crane *et al.*[31] give m. p. 155°.

[25] Lucas and Garner, *J. Amer. Chem. Soc.*, 1950, **72**, 2145.
[26] Nesmayanov and Lutsenko, *Bull. Acad. Sci. U.R.S.S. Classe Sci. chim.*, 1942, 366 (*Chem. Abs.*, 1945, **39**, 1637).
[27] Schalit, *Chem. Zentr.*, 1931, **102**, I, 2602.
[28] Kilmers, Armstrong, Brown, and du Vigneaud, *J. Biol. Chem.*, 1947, **145**, 495.
[29] Newbold, *J.*, 1950, 3346.
[30] Heilbron, Jones, and O'Sullivan, *J.*, 1946, 866.
[31] Crane, Forrest, Stephenson, and Waters, *J.*, 1946, 827.

The dichloro- and dibromo-DL-threitol derivatives were water-soluble and the derived halogenoacetaldehydes were much more stable than was the iodo-derivative. The 2,4-dinitrophenylhydrazones of chloro- and bromo-acetaldehyde were not formed readily. Heating to 80° for 10—15 min. accelerated the formation of chloroacetaldehyde 2,4-dinitrophenylhydrazone but resulted in replacement of bromine by chlorine in an attempt to prepare bromoacetaldehyde 2,4-dinitrophenylhydrazone. No depression of m. p. occurred with mixtures of chloro- and bromo-acetaldehyde 2,4-dinitrophenylhydrazones but their infrared spectra (potassium chloride discs) showed marked differences.

(*b*) Aqueous 0·075M-sodium metaperiodate solutions (100 ml.) severally containing 1,4-dichloro-1,4-dideoxy-DL-threitol (0·1088 g.), 1,4-dibromo-analogue (0·1696 g.), and 1,4-di-iodo-analogue (0·2342 g.) were stored at room temperature in the dark. The consumption of periodate was followed by essentially the method of Jackson [32] and was as shown in Table 1. Determination of formaldehyde by chromotropic acid [33] after 550 and 1375 hr. indicated that none had been formed. The hydrogen ion liberated after 1350 hr. was as follows: di-iodo-compound 1·09, di-bromo-compound 0·85, dichloro-compound 0·75 g.-ion per mole.

TABLE 1. *Consumption of periodate by the* 1,4-*dideoxy*-1,4-*dihalogeno*-DL-*threitols.*

Time (hr.)	3	17	45	72	142	196	305	545	838	1349	2016
Consumption of periodate (mol.):											
di-iodo-	1·8	2·19	2·91	3·80	5·22	5·92	6·84	8·44	9·26	9·97	10·66
dibromo ...	1·11	1·17	—	1·24	1·33	1·35	1·37	1·70	1·89	2·03	2·41
dichloro ...	1·04	1·08	1·10	1·14	1·17	1·19	1·25	1·46	1·58	1·70	2·18

Miscellaneous Periodate Oxidations.—Aqueous 0·0625M-sodium metaperiodate solutions (100 ml.) severally containing sodium β-hydroxypropionate [prepared by titration of β-propiono-lactone (0·05 g.) with 4N-sodium hydroxide] and β-aminopropionic acid (0·0626 g.) were prepared; the pH of the solutions were 5·7 and 5·1. Duplicate solutions were also prepared of which the pH was adjusted to 2·0—2·5. All the solutions were stored at 33° in the dark. Periodate was not consumed in the solutions at *ca.* pH 5 and was as follows in the solutions at pH 2·0—2·5:

Time (days)	Consumption of periodate (mol.)		Formaldehyde liberation (mol.)	
	A	*B*	*A*	*B*
3·15	—	0·04	—	0·02
10·15	0·02	0·12	0·006	0·03
75·0	0·25	0·76	—	—

A, β-Aminopropionic acid; *B*, β-hydroxypropionic acid.

Schwarz and MacDougall [5] have found that the determination of periodate, in the presence of benzyloxymalondialdehyde and related compounds, by titration with arsenite of the iodine liberated after addition of sodium hydrogen carbonate and iodide, gives unreliable results. Anomalous results were not encountered with Jackson's method [32] in its applications in this paper.

In a separate experiment a solution of aldol (1·4 mmoles) in 0·0625M-sodium metaperiodate was set aside at room temperature; the solution had pH 4—5. The consumption of oxidant was as follows: [32]

Time (days)	2	4	7
Consumption of periodate (mol.)	0·07	0·10	0·13

Influence of Certain 1,3-, 1,4-, 1,5-, *and* 1,6-*Diols on the* pH *of Aqueous Periodic Acid.*—Most of the diols listed in the Table were obtained by purification of commercial samples. In the case of propane-1,3-diol and butane-1,3-diol the samples were contaminated with appreciable amounts of impurities which consumed periodate. The diols were purified by dissolution in

[32] Jackson, *Organic Reactions*, 1944, **2**, 341.
[33] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.

water and treatment with a calculated excess of sodium metaperiodate for 30 min. at room temperature. After one extraction with benzene, the aqueous solution was continuously extracted with ether for 48 hr., the ether extract concentrated, and the residue distilled. The initial sample of propane-1,3-diol also contained a water-insoluble impurity which was removed by a single ether-extraction of the aqueous solution before the periodate oxidation stage. Pentane-2,4-diol, which presumably contains a mixture of DL- and *meso*-forms, was obtained by hydrogenation of acetylacetone and contained a trace of carbonyl compound as shown by the weak absorption at 1700 cm.$^{-1}$. The cyclohexane-1,3-diols were gifts from Dr. W. Rigby of Birkbeck College. The physical constants recorded in the Table are in reasonable agreement with values in the literature. With one exception, the purified diols did not react with periodate or contain acidic products; a 0·02713M-solution of *cis*-but-2-ene-1,4-diol in 0·06132M-sodium metaperiodate at 39° showed the following oxidant consumption: 48 hr. 0·083 mol., 120 hr. 0·253 mol., 502 hr. 0·65 mol.

The pH changes were measured as follows: separate aqueous solutions *A* and *B*, of 0·0255M-sodium metaperiodate which were also respectively *ca.* 0·025M and *ca.* 0·1M with respect to diol, were prepared and stored in the dark at room temperature for 48 hr. The pH of the solutions was then determined by using an E.I.L. direct reading pH meter (Model 23A) calibrated against potassium hydrogen phthalate (pH 4). The arithmetical difference between the pH's of solution *A* and *B* and 0·0255M-sodium metaperiodate are expressed respectively as ΔpH (*A*) and ΔpH (*B*), and are recorded in Table 2. The values represent the average of several determinations. A negative value of ΔpH indicates a depression of the pH.

TABLE 2. *Physical constants and* ΔpH *values for some diols.*

	B. p./mm.[a] or m. p.	n^{20}	ΔpH (*A*)	ΔpH (*B*)
Propane-1,3-diol	72—74°/0·15	1·4388	−0·22	−0·49
Butane-1,3-diol	85—86°/1	1·4395	−0·06	−0·14
Pentane-2,4-diol	76—77°/0·7—0·8	1·4339	−0·57	−0·89
2,2-Dimethylpropane-1,3-diol	129—131°	—	−0·04	−0·04
Pentaerythritol	255—257°	—	−0·23	−0·36
Butane-1,4-diol	91—92°/0·4—0·5	1·4459	−0·10	−0·27
cis-But-2-ene-1,4-diol	96—99°/0·4—0·6	1·4771	−0·92[b]	−1·92
Pentane-1,5-diol	100°/0·3—0·4	1·4510	−0·00	+0·02
Hexane-1,6-diol		—	−0·02	−0·04
Cyclohexane-*cis*-1,3-diol	86°	—	−0·04	+0·08
Cyclohexane-*trans*-1,3-diol	117°	—	−0·06	−0·05

[a] Vapour temperature given. [b] Determined after 5 min.

The pH's of aqueous periodic acid solutions 0·025M (pH 1·86), 0·0025M (pH 2·61), and 0·00025M (pH 3·57) were not significantly changed when the solutions were also *ca.* 0·025M and *ca.* 0·1M with respect to pentaerythritol. There was also no significant effect in 0·00025M-periodic acid solutions which were also *ca.* 0·025M with respect to, 2,2-dimethylpropane-1,3-diol, butane-1,3-diol, butane-1,4-diol, *cis*-but-2-ene-1,4-diol, propane-1,3-diol, and pentane-1,5-diol.

The authors thank Professor M. Stacey, F.R.S., for his interest in this work. One of them (J. L. B.) was able to participate in the work under the auspices of the Colombo Plan.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, April 6th,* 1959.]

673. *The Constitution and Stereochemistry of Drimenol, a Novel Bicyclic Sesquiterpenoid.*[1]

By H. H. Appel, C. J. W. Brooks, and K. H. Overton.

The constitution and absolute stereochemistry of the sesquiterpenoid drimenol, $C_{15}H_{26}O$, obtained from the bark of *Drimys winteri* Forst. have been elucidated. The saturated drimanic and drimic acid previously obtained are shown to be identical with two known degradation products, $C_{15}H_{28}O_2$ from oleanolic acid or ambrein, and $C_{12}H_{20}O_4$ from abietic acid or onocerin. Drimenol is the first bicyclic sesquiterpenoid having the structure and absolute stereochemistry characteristic of rings A and B of the di- and tri-terpenoids. This fact has theoretical significance in the biogenesis of terpenoids.

Drimenol was isolated in 1948 from the bark of *Drimys winteri* Forst. by Appel and his collaborators [2]; it was shown to be a mono-olefinic bicyclic primary alcohol, since it consumed one mol. of peracid and on catalytic hydrogenation furnished a saturated dihydro-alcohol, drimanol, which was oxidised by Beckmann's mixture without loss of carbon to a monocarboxylic acid, drimanic acid. Oxidation of drimenol with the same reagent gave a ketone, drimone (characterised as the oxime), which could be further oxidised to a saturated dicarboxylic acid, drimic acid. A consideration of analytical values suggested for drimenol the composition $C_{16}H_{28}O$, for drimone $C_{14}H_{22}O$ and for drimic acid $C_{12}H_{20}O_4$. A continuation of these studies has now led to the elucidation of the structure and stereochemistry of drimenol.

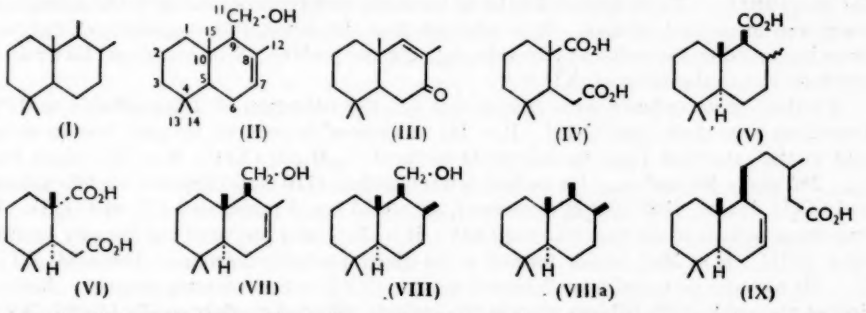
The previous data can be supplemented as follows. Drimenol further revealed its unsaturated nature in its ultraviolet ($\varepsilon_{210\,m\mu}$ 2140; $\varepsilon_{215\,m\mu}$ 950; $\varepsilon_{220\,m\mu}$ 250) and its infrared absorption ($\nu_{max.}$ 814 cm.$^{-1}$ in Nujol): these are characteristic of a triply substituted ethylenic linkage.[3,4] Moreover, drimenol gave a yellow colour with tetranitromethane, and was oxidised by monoperphthalic acid to a saturated crystalline epoxy-alcohol (see below), m. p. 96—97°, which showed no selective absorption between 210 and 300 mμ and in the infrared had (in Nujol) $\nu_{max.}$ 3400 cm.$^{-1}$ (associated OH) but no bands in the carbonyl region. Drimenol was recovered unchanged after treatment with manganese dioxide [5] in chloroform, and thus appeared not to be an allylic alcohol. Drimone was disclosed as an αβ-unsaturated ketone by its ultraviolet absorption ($\lambda_{max.}$ 235 mμ; ε 6500) whilst its infrared absorption (in CCl_4) ($\nu_{max.}$ 1670 cm.$^{-1}$) suggested that the chromophore was situated in a six-membered ring.

Our initial efforts were directed towards establishment of the carbon skeleton of drimenol. Dehydrogenation on palladised charcoal at 350° afforded as the sole identified product 1,2,5-trimethylnaphthalene, in about 30% yield. Our immediate inference was that we were dealing with a compound possessing the C_{15} carbon skeleton (I) normally found in rings A and B of the di- and tri-terpenoids. On this assumption, coupled with the evidence already presented, we were compelled to reformulate drimenol as $C_{15}H_{26}O$ and to assign to it the structure (II), particularly in order to accommodate the transformations into drimone (III) and into drimic acid (IV). This conclusion was strengthened by a comparison of the physical constants of drimanic (driman-11-oic acid *) and drimic acid

* We propose the name drimane for the saturated hydrocarbon having the structure and stereochemistry depicted in (VIIIa). The numbering follows the system proposed by Djerassi *et al.*[6]

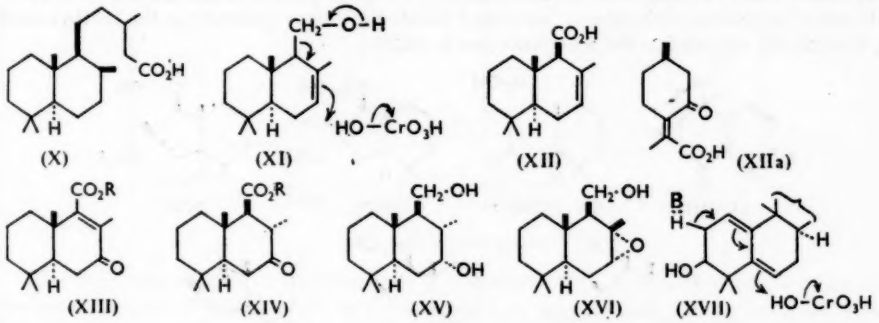
[1] Preliminary communication: Brooks and Overton, *Proc. Chem. Soc.*, 1957, 322.
[2] Appel, Gleisner, and Sahli, *Scientia (Chile)*, 1948, **15**, 31; Appel, Rotman, and Thornton, *ibid.* 1956, **23**, 19.
[3] Halsall, *Chem. and Ind.*, 1951, 867; Bladon, Henbest, and Wood, *J.*, 1952, 2737.
[4] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1958, p. 51.
[5] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.
[6] Djerassi, Rittel, Nussbaum, Donovan, and Herran, *J. Amer. Chem. Soc.*, 1954, **76**, 6410.

with those recorded for the acids $C_{15}H_{26}O_2$ (V) (previously obtained from oleanolic acid and ambrein [7]) and $C_{12}H_{20}O_4$ (VI) (from onocerin and abietic acid [8]), respectively. Direct comparison subsequently confirmed these identities,* establishing the structure and absolute stereochemistry of drimenol as in (VII), if we make the reasonable assumption that no migration of the ethylenic linkage occurs during the hydrogenation of drimenol. Dr. A. Eschenmoser (Zurich) has kindly informed us that the infrared spectra of drimenol and α-bicyclofarnesol (in chloroform) are identical, thus confirming our assignment of configuration at $C_{(9)}$. We formulate drimanol as (VIII), the configuration at position 8 being tentatively assigned on the following grounds: (i) drimanol is the major product of hydrogenation, which would be expected to occur from the less hindered α-face, as in the



case [9] of cativic acid (IX); (ii) similar molecular rotation changes are associated with the hydrogenation of drimenol to drimanol (ΔM_D +73°) and of cativic acid to dihydrocativic acid (X) (ΔM_D +98°).

The genesis of " drimone " (renamed nordrimenone; systematically 11-nordrim-8-en-7-one) in the oxidation of drimenol with chromic acid or potassium dichromate in aqueous acetic acid (see p. 3322) may be considered to take place as in (XI) (arrows): a formal resemblance to the formation of oleanone from moradiol [10] is worthy of note. The proposed constitution of nordrimenone is further substantiated by its conversion into



drimic acid on ozonolysis; † the concomitant formation of acetic acid could be confirmed by its conversion into *p*-bromophenacyl acetate and by the infrared spectrum of the derived sodium acetate.

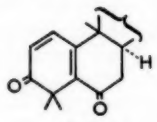
We now turn briefly to two further aspects of drimenol chemistry.

* We are grateful to Professors E. Lederer (Paris) and O. Jeger (Zurich) for authentic samples.
† This reaction provides a convenient alternative preparation of drimic acid.

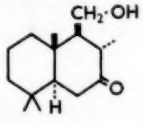
[7] Ruzicka, Gutmann, Jeger, and Lederer, *Helv. Chim. Acta*, 1948, **31**, 1746.
[8] Schaffner, Viterbo, Arigoni, and Jeger, *ibid.*, 1956, **39**, 174.
[9] Grant and Zeiss, *J. Amer. Chem. Soc.*, 1954, **76**, 5001.
[10] Barton and Brooks, *J.*, 1951, 257.

The first arose in an attempt to prepare drim-7-en-11-oic acid[7] (XII) from drimenol with chromium trioxide–pyridine[11] followed by silver oxide, in order to confirm our assignment of the ethylenic linkage in drimenol. The only crystalline compound directly isolated from the first reaction, in 12—15% yield, was a singly unsaturated, ketonic carboxylic acid, $C_{15}H_{22}O_3$, to which we assign the constitution (XIII; R = H) for the following reasons. The compound (in carbon tetrachloride) showed bands at 1685 (αβ-unsaturated cyclohexenone), 1748 (CO_2H) and 2800—2300 cm.$^{-1}$ (associated OH of CO_2H). In neutral ethanol it had $\lambda_{max.}$ 247 mμ (ε 8500) and 323 mμ (ε 42), but in 0·001N-ethanolic sodium hydroxide at room temperature it immediately showed $\lambda_{max.}$ 260 mμ (ε 11,600) whilst in 0·001N-ethanolic hydrochloric acid there was a slight hypsochromic shift [$\lambda_{max.}$ 241 mμ (ε 9400)]. There appeared to be an isosbestic point corresponding to the absorption maximum in neutral ethanol. It is relevant that the autoxidation product of menthofuran has, in ethanolic sodium hydroxide, $\lambda_{max.}$ 265 mμ (ε 8500); Woodward and Eastman[12] attribute this to the anion of (XIIa).

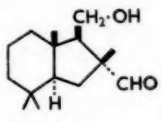
Further, in accordance with expectation (cf. the reduction of 7-keto-Diels's acid[13]), 7-oxodrim-8-en-11-oic acid (XIII; R = H) was smoothly reduced by zinc dust in acetic acid to the saturated 7-oxo-8α-driman-11-oic acid, $C_{15}H_{24}O_3$ (XIV; R = H), which had $\lambda_{max.}$ 282 mμ (ε 40) and $\nu_{max.}$ (in carbon tetrachloride), 1710 (superimposed cyclohexanone and CO_2H dimer), 1752 (CO_2H monomer), and 3525 cm.$^{-1}$ (unbonded OH of CO_2H). It was characterised as the methyl ester (XIV; R = Me) [also prepared *via* the oily methyl ester (XIII; R = Me)] which formed a 2,4-dinitrophenylhydrazone. The acid (XIV; R = H) was also prepared from drimenol α-oxide (XVI) in the following manner. Reduction of the oxide with lithium aluminium hydride afforded 8α-drimane-7α,11-diol (XV): the production of the secondary alcohol (see below) indicates the α-configuration of the oxide and permits the assignment of configuration at position 8 in the diol. Oxidation of the diol (XV) with chromic acid in acetic acid afforded the oxo-acid (XIV; R = H), thus securing the stereochemistry of this acid at positions 8 and 9, it being assumed that the equatorial position for the 8-methyl group is more stable than the axial. In agreement with this formulation, the oxo-acid (XIV; R = H) was not reconverted into the acid (XIII; R = H) by selenium dioxide in refluxing ethanol. Clearly the initial *cis*-addition product[14] of zinc reduction of the acid (XIII; R = H) is partly isomerised to (XIV; R = H) before or during working-up; a product isolated in minor quantity as the methyl ester is tentatively regarded as the 8β-epimer (see p. 3328).



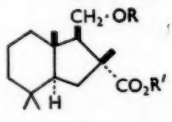
(XVIII)



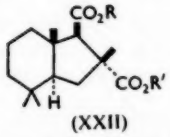
(XIX)



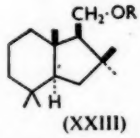
(XX)



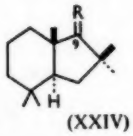
(XXI)



(XXII)



(XXIII)



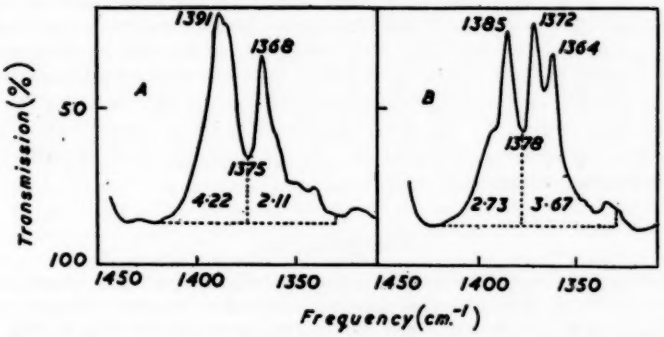
(XXIV)

The genesis of the acid (XIII; R = H) clearly bears some analogy to that of nordrimenone. A parallel example of the attack of chromium trioxide–pyridine on an ethylenic linkage is the conversion[15] of alnusadienol (XVII) into the dienedione (XVIII).

[11] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[12] Woodward and Eastman, *ibid.*, 1950, **72**, 399.
[13] Windaus, *Ber.*, 1908, **41**, 611.
[14] Zimmerman, *J. Amer. Chem. Soc.*, 1957, **79**, 6554, and earlier papers there cited.
[15] Beaton, Spring, Stevenson, and Stewart, *Tetrahedron*, 1958, **2**, 246.

A projected route to the compound (XIV) led to another interesting reaction. Thus, the boron trifluoride–ether complex might have been expected [16] to convert drimenol α-oxide (XVI) into the hydroxy-ketone (XIX). In fact this reagent produced an oily isomeric hydroxy-aldehyde, $C_{15}H_{26}O_2$ (characterised as the 2,4-dinitrophenylhydrazone), which on the basis of the spectroscopic data and subsequent transformations must be formulated as (XX). Thus it had infrared bands in carbon tetrachloride at 1728 and 2700 (saturated aliphatic CHO) and 3480 and 3600 cm.$^{-1}$ (OH) and an ultraviolet maximum at 280 mμ (ε ~12), whilst the 2,4-dinitrophenylhydrazone had $\lambda_{max.}$ 358 mμ (ε 25,000). Oxidation with silver oxide furnished the hydroxy-acid, $C_{15}H_{26}O_3$ (XXI; R = R′ = H) [$\nu_{max.}$ (in Nujol) 1703 (CO_2H dimer), 3220 (associated OH), and 2630 cm.$^{-1}$ (associated OH of CO_2H)], characterised as the acetate (XXI; R′ = H, R = Ac). Oxidation of the acid (XXI; R = R′ = H) with chromium trioxide in acetic acid afforded the dicarboxylic acid (XXII; R = R′ = H) [$\nu_{max.}$ (in Nujol) 1703 (CO_2H; dimer) and 3200—2600 cm.$^{-1}$ (associated OH of CO_2H)], characterised as its dimethyl ester (XXII; R = R′ = Me) [$\nu_{max.}$ (in CCl_4) 1743 cm.$^{-1}$ (ester CO)]. Similar oxidation of the oily ester (XXI; R = H, R′ = Me) gave the monomethyl ester (XXII; R = H, R′ = Me) [($\nu_{max.}$ (in Nujol)] 1730 (ester CO), 1705 (CO_2H dimer), and 3180—2650 cm.$^{-1}$ (OH of CO_2H)]. Attempts to convert the acid (XXII; R = R′ = H) into the anhydride by sublimation or by treatment with acetic anhydride were unsuccessful. Likewise the acid (XXI; R = R′ = H) showed no tendency to form a lactone. This is fully in accordance with the stereochemistry assigned to (XXII) on its mode of formation from the oxide (XVI). The rearrangement of cyclohexene epoxides is known to occur with ring contraction in sterically favourable examples.[17] The nature of the carbon skeleton of (XX) was finally secured in the following way. Wolff–Kishner reduction gave the crystalline isodrimanol (XXIII; R = H) which was not identical either with drimanol or with 8α-drimanol (which is a minor product in the hydrogenation of drimenol; see p. 3329).

Infrared spectra of (A) drimanol and (B) isodrimanol.



The structure assigned to isodrimanol is supported by a comparison of the infrared spectra of drimanol, 8α-drimanol, and isodrimanol in the region of absorption associated with the symmetrical CH deformation mode (" breathing ") of methyl groups. We are greatly indebted to Dr. G. Eglinton and Mr. J. F. Morman for the following observations and their interpretation.

Drimanol and 8α-drimanol showed very similar absorption (in carbon tetrachloride) over the region 1500—1300 cm.$^{-1}$, the main peaks being at 1469, 1460, 1445, 1391, and 1368 cm.$^{-1}$. Isodrimanol, however, showed marked differences, particularly in the methyl " breathing " region, the main peaks being at 1466, 1385, 1372, and 1364 cm.$^{-1}$ (Figure).

[16] Henbest and Wrigley, *J.*, 1957, 4596.
[17] See, *inter al.*, House and Wassen, *J. Amer. Chem. Soc.*, 1957, **79**, 1488; Naqvi, Horwitz, and Filler, *ibid.*, p. 6283.

" Breathing " vibrations of different types of methyl groups have been quoted [18,19] as occurring at the following frequencies: *gem*-dimethyl 1384 and 1364 cm.$^{-1}$; angular methyl (6,6 ring fusion) 1385 $\pm$ 9 cm.$^{-1}$ (6,5 ring fusion), 1377 $\pm$ 5 cm.$^{-1}$; ordinary methyl 1380 $\pm$ 6 cm.$^{-1}$. Thus in isodrimanol the two peaks at 1372 and 1364 cm.$^{-1}$ must represent the lower-frequency components of the CH deformations of the two differently situated *gem*-dimethyl groups: the group attached to the six-membered ring evidently gives rise to a peak slightly displaced from its position in drimanol and 8α-drimanol, presumably as a consequence of the contraction of the attached ring, whilst the second peak must be due to the new *gem*-dimethyl group arising from the contraction. The absorption due to the angular methyl group in isodrimanol is evidently contained in the peak at 1385 cm.$^{-1}$. A more detailed analysis of the bands in this region is probably unjustified in view of the considerable steric interactions between the various methyl substituents in all three alcohols.

The regions of absorption attributed to the lower component of the *gem*-dimethyl " breathing " mode were taken to range between the relevant minima of the absorption curves. For drimanol this region was 1375—1330 and for isodrimanol 1378—1330 cm.$^{-1}$. The apparent integrated absorption intensities (β) were found to be in the ratio of 1 : 1·74 in satisfactory agreement with the expected 1 : 2 relation.

The ratio of integrated absorption intensities over the region 1420—1330 cm.$^{-1}$ for drimanol and isodrimanol was almost unity though there are four methyl groups in the former and five in the latter. Evidently for this region β/2 for *gem*-dimethyl is somewhat less than β for an isolated methyl group.

Conversion of the alcohol (XXIII; R = H) by pyrolysis of its acetate (XXIII; R = Ac) [$\nu_{max.}$ (in Nujol) 1746, 1240 cm.$^{-1}$ (acetate)] into isodrim-9-ene (XXIV; R = CH_2) [$\nu_{max.}$ 880, 1645 cm.$^{-1}$ (=CH_2)] and ozonolysis afforded isonordrimanone (XXIV; R = O) which had $\nu_{max.}$ 1738 cm.$^{-1}$ (CO of cyclopentanone).

Three examples are now known of the novel class of sesquiterpenoid represented by drimenol. Of these iresin [20] and farnesiferol A [21] have the same skeletal structure as drimenol but are of the opposite absolute configuration (which is also found in the diterpenoids eperuic acid [22] and cafestol [23]). Drimenol is thus the first representative of this class possessing both the skeletal structure and absolute stereochemistry normally found in rings A and B of the di- and tri-terpenoids, and so constituting a biogenetic link between these three groups.[24] The intermediacy of drimenol gains further significance from the cyclisation of farnesylic acid *in vitro* to drimenic acid, recently clarified by Stadler, Eschenmoser, Schinz, and Stork.[25]

Experimental

Ultraviolet absorption spectra were determined with the Unicam S.P. 500 spectrophotometer and are for solutions in ethanol unless specified otherwise. Routine infrared spectra were kindly determined with the Perkin–Elmer 13 spectrophotometer by Mrs. F. Lawrie. Microanalyses were carried out by Mr. J. M. L. Cameron and his associates. The light petroleum used was of b. p. 60—80° unless stated to the contrary. Chromatographic alumina was prepared and standardised by Brockmann's procedure.[26]

[18] (*a*) Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5648; (*b*) Jones and Sandorfy, Chapter 4 in " Techniques of Organic Chemistry," Vol. IX, Interscience Publ. Inc., New York, 1956.
[19] Bottomley, Cole, and White, *J.*, 1955, 2624.
[20] Djerassi and Burstein, *J. Amer. Chem. Soc.*, 1958, **80**, 2593; Rossmann and Lipscomb, *ibid.*, p. 2592.
[21] Caglioti, Naef, Arigoni, and Jeger, *Helv. Chim. Acta*, 1958, **41**, 2278.
[22] King and Jones, *J.*, 1955, 658; Cocker and Halsall, *J.*, 1956, 262; Djerassi and Marshall, *Tetrahedron*, 1958, **1**, 247.
[23] Djerassi, Cais, and Mitscher, *J. Amer. Chem. Soc.*, 1958, **80**, 247.
[24] Ruzicka, *Experientia*, 1953, **9**, 357.
[25] Stadler, Eschenmoser, Schinz, and Stork, *Helv. Chim. Acta*, 1957, **40**, 2191.
[26] Brockmann, *Ber.*, 1941, **74**, 73.

Extraction of Drimenol.—The air-dried powdered bark was extracted exhaustively with light petroleum (b. p. 70—80°) in a Soxhlet apparatus. The light brown viscous oil (45% of the weight of bark) obtained after removal of the solvent afforded on distillation *in vacuo* a viscous yellow fraction (b. p. 120—195°/8 mm.) which crystallised. Crude drimenol (13% by weight of the extract) was obtained by filtration and washing with a little benzene. Recrystallised from light petroleum, it formed prisms, m. p. 97—98°, $[\alpha]_D$ −18° (*c* 3·55 in benzene), giving a positive reaction with tetranitromethane, $\nu_{max.}$ 3570 (free OH), 3450 (bonded OH) cm.$^{-1}$ in CS_2 (Found: C, 80·75; H, 11·7. Calc. for $C_{15}H_{26}O$: C, 81·0; H, 11·8%).

Recent experiments (H. H. Appel and R. Dohr [27]) have shown that drimenol is not an invariable constituent of the bark of Chilean *Drimys winteri* Forst. The first sample investigated happened to be particularly rich in this alcohol. Of fifteen barks obtained from different parts of the country, drimenol has been found in only four.

When a solution of drimenol (120 mg.) in chloroform (10 ml.) was shaken with manganese dioxide (1 g.) for 3 hr. there was no significant change in light absorption, and drimenol (80 mg.) was recovered.

Dehydrogenation of Drimenol.—Drimenol (1 g.) was heated with 5% palladised charcoal (1 g.) for 1 hr. at 300—350° in a stream of carbon dioxide. The hydrogen evolved amounted to 105 ml. (calc. for complete dehydrogenation, 300 ml.). Extraction of the residue with ether afforded a yellow oil (360 mg.) which appeared, from its ultraviolet absorption (principal $\lambda_{max.}$ 229 mμ, $E^{1\%}_{1cm.}$ 2780) to be substantially 1,2,5-trimethylnaphthalene. Portions were converted into the styphnate (recrystallised from ethanol–light petroleum), m. p. 126—128° (evacuated capillary) undepressed on admixture with authentic material of m. p. 127—129°, and into the 1,3,5-trinitrobenzene adduct [from ether–light petroleum (b. p. 40—60°)], m. p. 153—156° (evacuated capillary) undepressed on admixture with authentic material of the same m. p. The identity of the latter adduct with authentic material was confirmed by the infrared absorption (in Nujol). A portion of the isolated trinitrobenzene adduct was decomposed on alumina (activity I), yielding crystalline 1,2,5-trimethylnaphthalene, identified by m. p., mixed m. p., and infrared absorption (film).

Drimenol α-Oxide.—A solution of drimenol (1·22 g., 5·5 mmoles) in ether (25 ml.) was mixed with one of monoperphthalic acid in ether (25 ml.; 0·34M) and left at 5° for 67 hr. The mixture was poured into ice (100 g.), ethanol (50 ml.), sodium dithionate (3 g.), and N-sodium hydroxide (50 ml.), and the ether was removed at room temperature. The single alkaline phase so obtained was extracted with ether, and the extracts were washed with water, dried (Na_2SO_4), and evaporated. The residue crystallised from ether–light petroleum as prisms (635 mg., 49%), m. p. 96—97°. The mother-liquor gave a second crop (292 mg., 22%), m. p. 95—96°. The pure *oxide* had m. p. 96—97°, $[\alpha]_D$ +20° (*c* 1·56 in chloroform), and gave no colour with tetranitromethane (Found: C, 75·7; H, 10·65. $C_{15}H_{26}O_2$ requires C, 75·55; H, 11·0%). Drimenol α-oxide showed no selective absorption between 210 and 300 mμ.

8α-Drimane-7α,11-diol.—A solution of drimenol α-oxide (300 mg., 1·22 mmoles) in dry tetrahydrofuran (20 ml.) was added dropwise during 0·5 hr. to refluxing tetrahydrofuran (50 ml.) containing lithium aluminium hydride (600 mg.). Refluxing was continued for 21 hr. The mixture was cooled and treated successively with ethyl acetate, aqueous acetic acid, ice, and finally 2N-sulphuric acid (6 ml.) to give pH ~5. Ether-extraction afforded a solid (300 mg.), m. p. 140—146°, recrystallised from chloroform–light petroleum as prisms (146 mg., 48%), m. p. 154—155°, $[\alpha]_D$ −17° (*c* 1·15 in chloroform) (Found: C, 74·9; H, 11·6. $C_{15}H_{28}O_2$ requires C, 74·95; H, 11·75%). A second crop was purified by sublimation at 150°/1 mm., giving material (98 mg., 32%) of m. p. 150—152°.

Oxidation of Drimenol with Chromium Trioxide–Pyridine.—Drimenol (3 g.) in dry pyridine (30 ml.) was mixed with a suspension of the reagent prepared from chromium trioxide (7·5 g.) and dry pyridine (75 ml.). The mixture was left for 2·5 hr. at room temperature with occasional shaking and then poured into cold water (250 ml.). After the excess of oxidant had been destroyed by sulphur dioxide, the solution was extracted with benzene–ethyl acetate (1 : 1). The combined extracts were washed successively with water, four times with 2N-hydrochloric acid, and again with water, then dried (Na_2SO_4) and evaporated, yielding an amber gum (2·76 g.). This was chromatographed on alumina (activity V; 50 g.), giving two major fractions: (i) an intractable oil (1450 mg.), eluted at once by light petroleum (b. p. 40—60°), and (ii) a mainly crystalline fraction (680 mg.) eluted immediately after (i) by the same solvent. Fraction (i)

[27] Appel and Dohr, *Scientia* (*Chile*), 1958, **25**, 137.

was rechromatographed on alumina (activity III; 40 g.) but no crystalline material could be isolated, and there was evidence of decomposition on the column. The ultraviolet absorption of various fractions from the rechromatography showed them to be crude αβ-unsaturated ketones ($\lambda_{max.}$ 235—242 mμ) but the highest intensity obtained was only $E^{1\%}_{1\,cm.}$ 170, *i.e.*, only about half that expected for a pure compound. Fractional distillation at 1 mm. afforded only partial concentration ($\lambda_{max.}$ 235 mμ, $E^{1\%}_{1\,cm.}$ ~220), and the material was converted into the 2,4-dinitrophenylhydrazone which crystallised from ether–ethanol as orange needles, m. p. 174—175°, which became orange-red in air (Found: C, 62·1; H, 6·6; N, 15·35. $C_{20}H_{26}O_4N_4$ requires C, 62·15; H, 6·8; N, 14·5%), $\lambda_{max.}$ (in chloroform) 382—383 mμ (ε 28,000), (in 99 : 1 ether–chloroform) 366—367 mμ (ε 30,000). Fraction (ii), recrystallised from ether–light petroleum, yielded prisms (360 mg.), m. p. 222—224°, $[\alpha]_D$ +47° (*c* 1·70 in chloroform) (Found: C, 72·3; H, 9·0. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%). In several experiments the yield of this *product* remained low. Infrared bands of the oily methyl ester in carbon tetrachloride were at 1680 (αβ-unsaturated cyclohexenone), 1730 cm.$^{-1}$ (ester CO).

Reduction of 7-Oxodrim-8-en-11-oic Acid with Zinc and Acetic Acid.—The unsaturated keto-acid (286 mg.) in glacial acetic acid (20 ml.) was refluxed with zinc dust (6 g.) for 10 min. The mixture was worked up in the normal way, to yield *7-oxo-8α-driman-11-oic acid* (260 mg.) which crystallised from ether–light petroleum (b. p. 40—60°) as prisms, m. p. 202—203° (140 mg.), $[\alpha]_D$ +1° (*c* 0·76 in chloroform) (Found: C, 71·3; H, 9·55. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). The *methyl ester*, prepared with diazomethane and recrystallised from aqueous methanol, formed prisms, m. p. 73·5—74° (Found: C, 72·05; H, 9·75. $C_{16}H_{26}O_3$ requires C, 72·15; H, 9·85%), $\nu_{max.}$ (in carbon tetrachloride) 1730 and 1710 cm.$^{-1}$. This ester was also obtained by zinc reduction of the oily methyl 7-oxodrim-8-en-11-oate. It formed a *2,4-dinitrophenylhydrazone*, golden-yellow needles (from aqueous ethanol), m. p. 166—168° (Found: C, 59·4; H, 6·4; N, 12·55. $C_{22}H_{30}O_6N_4$ requires C, 59·2; H, 6·75; N, 12·55%), $\lambda_{max.}$ (in chloroform) 363 mμ (ε 23,500), $\nu_{max.}$ (in carbon tetrachloride) 1732 cm.$^{-1}$.

The uncrystallisable residue (150 mg.) from two preparations of 7-oxo-8α-driman-11-oic acid was methylated by diazomethane. Chromatography on alumina (activity III) gave two main ketonic fractions: (i) (52 mg.), eluted by light petroleum, identified as methyl 7-oxo-8α-driman-11-oate by conversion into the 2,4-dinitrophenylhydrazone, and (ii) (67 mg.), eluted by light petroleum–benzene (1 : 1) as an oil which yielded, after sublimation *in vacuo*, crystals, m. p. 60—61° (Found: C, 72·2; H, 9·4. Calc. for $C_{16}H_{26}O_3$: C, 72·15; H, 9·85%), $\nu_{max.}$ (in carbon tetrachloride) 1717 and 1735 cm.$^{-1}$, further characterised as a *2,4-dinitrophenylhydrazone*, needles (from ethyl acetate–light petroleum), m. p. 197—198° (Found: C, 59·4; H, 6·5; N, 12·8. $C_{22}H_{30}O_6N_4$ requires C, 59·2; H, 6·75; N, 12·55%), $\lambda_{max.}$ (in chloroform) 370 mμ (ε 23,600), $\nu_{max.}$ (in carbon tetrachloride) 1732 cm.$^{-1}$. This second ketonic ester is tentatively regarded as methyl 7-oxo-8β-driman-11-oate. The infrared spectra of the two oxo-esters and of their dinitrophenylhydrazones are consonant with the structures proposed.

Oxidation of 8α-Drimane-7α,11-diol by Chromic Acid.—The diol (98 mg., 0·38 mmole) was dissolved directly in a 0·062N-solution of chromium trioxide (30 ml.) in 99·8% acetic acid. The oxidant was rapidly consumed, 1·85 " atoms of oxygen " being consumed within 20 min. and only a further 0·05 in the next 40 min. Worked up at this stage the solution gave as the only crystallisable product 7-oxo-8α-driman-11-oic acid (42 mg.), identical by m. p., mixed m. p., and infrared spectrum with the product described above.

Treatment of Drimenol Oxide with Boron Trifluoride.—(i) Drimenol oxide (139 mg.) in 15 ml. of dry benzene was treated with freshly distilled boron trifluoride–ether complex (0·2 ml.). After 3 min. a spot test on paper indicated the presence of a carbonyl group, and the solution was shaken with saturated aqueous sodium hydrogen carbonate and extracted with benzene. The combined extracts were washed with water and evaporated, giving an oil (130 mg.) which failed to yield crystalline material when chromatographed on alumina. Fractions eluted by benzene (92 mg.) afforded a crystalline *2,4-dinitrophenylhydrazone*, recrystallising from aqueous ethanol as orange platelets, m. p. 171—172° (Found: C, 60·4; H, 7·45; N, 13·0. $C_{21}H_{30}O_5N_4$ requires C, 60·25; H, 7·25; N, 13·4%).

The hydroxy-aldehyde was further characterised as the *azine*, m. p. 188—189°, formed by treatment with hydrazine in refluxing aqueous ethanol and recrystallised from ether–light petroleum (Found: C, 76·75; H, 10·85; N, 6·1. $C_{30}H_{52}O_2N_2$ requires C, 76·2; H, 11·1; N, 5·95%), $\lambda_{max.}$ (in ethanol) 210 mμ (ε 19,000), $\nu_{max.}$ (Nujol mull) 1640 (C=N), 3400 and 3250 cm.$^{-1}$ (associated OH).

(ii) Drimenol oxide (300 mg.) in dry benzene (80 ml.) was treated with boron trifluoride–ether complex (0·50 ml.), and the solution was worked up as in (i) after 5 min. A solution of the crude product in ethanol (15 ml.) was added dropwise during 10 min. to a stirred suspension of silver oxide [prepared by the slow addition of 25% aqueous potassium hydroxide (8 ml.) to hot 7% aqueous silver nitrate (8 ml.) and heated on the steam-bath]. The mixture was stirred and heated under reflux for 30 min., left to cool, and filtered, and the filtrate was extracted with ether to remove non-acidic products (33 mg.). Acidification of the aqueous phase and further extraction afforded a mainly crystalline *hydroxy-acid* (240 mg.), recrystallising from ether–light petroleum as plates (163 mg., 51%), m. p. 172—173°, $[\alpha]_D$ +34° (*c* 1·15 in chloroform) (Found: C, 70·65; H, 10·5. $C_{15}H_{26}O_3$ requires C, 70·85; H, 10·3%). (In a second preparation the yield of pure product was 70%.) The corresponding *acetate*, prepared with acetic anhydride and pyridine, formed plates from ether–light petroleum and was further purified by sublimation (bath temp. 140°/1 mm.); it had m. p. 145—146°, $[\alpha]_D$ +15° (*c* 0·95 in chloroform) (Found: C, 69·1; H, 9·7. $C_{17}H_{28}O_4$ requires C, 68·9; H, 9·5%).

Oxidation of the Hydroxy-acid by Chromic Acid.—A solution of the hydroxy-acid (90 mg.; m. p. 172—173°) in acetic acid (5 ml.) was treated with chromium trioxide in acetic acid (10 ml.; 0·074N) and after 10 min. the mixture was worked up as usual to give a gummy *dicarboxylic acid* which crystallised from ether–light petroleum to yield prisms (35 mg.), m. p. 233—235°. Purification for analysis was conveniently effected by sublimation at 160°/0·1 mm. [Found: C, 67·45; H, 9·2; equiv. (potentiometric titration to first end-point) 271, (titration to second obscure end-point, pH ~11) 142. $C_{15}H_{24}O_4$ requires C, 67·15; H, 9·0%].

A similar oxidation of the oily methyl ester of the hydroxy-acid (prepared with diazomethane) yielded a *monomethyl ester* of the dicarboxylic acid, purified by sublimation (130°/0·5 mm.) and by recrystallisation from ether–light petroleum as prisms, m. p. 125—126° (Found: C, 68·05; H, 9·2. $C_{16}H_{26}O_4$ requires C, 68·05; H, 9·3%).

The dimethyl ester of the dicarboxylic acid, prepared with diazomethane and purified by recrystallisation from aqueous methanol and by sublimation (40°/0·4 mm.), had m. p. 47—48°, $[\alpha]_D$ −11° (*c* 0·63 in chloroform) (Found: C, 68·55; H, 9·35. $C_{17}H_{28}O_4$ requires C, 68·9; H, 9·5%).

Wolff–Kishner Reduction of the Crude Hydroxy-aldehyde from Boron Trifluoride Treatment of Drimenol Oxide.—The crude product, from the treatment of drimenol oxide (350 mg.) with boron trifluoride, as described above, was heated at 180° for 11 hr. with hydrazine hydrate (1 ml.), sodium ethoxide (300 mg.), and ethanol (2 ml.). The crude product (300 mg.) was chromatographed on alumina (15 g.) (activity III). The light petroleum eluates yielded plates (120 mg.) (from aqueous acetone), m. p. 80—81°, $[\alpha]_D$ +8° (*c* 0·95 in chloroform) (Found: C, 80·4; H, 12·45. $C_{15}H_{28}O$ requires C, 80·3; H, 12·6%). The *acetate*, prepared with acetic anhydride and pyridine, formed needles (from aqueous ethanol), m. p. 36°, $[\alpha]_D$ +14° (*c* 1·17 in chloroform) (Found: C, 76·9; H, 11·55. $C_{17}H_{30}O_2$ requires C, 76·75; H, 11·35%). The *toluene*-p-*sulphonate* formed needles (from aqueous acetone), m. p. 104—104·5°, $[\alpha]_D$ +16° (*c* 1·43 in chloroform), $\lambda_{max.}$ 225 mμ (ε 13,300) (Found: C, 70·0; H, 9·25. $C_{22}H_{34}O_3S$ requires C, 69·8; H, 9·05%).

Isodrimene.—Pyrolysis of isodrimanyl acetate (70 mg.) was effected by distilling it under nitrogen through a Pyrex tube (30 × 1 cm.) heated at 540°. The yellow condensate was freed from acetic acid, and the crude product (60 mg.) was chromatographed on alumina (15 g., grade V). Light petroleum (30 ml.) eluted isodrimene (32 mg.).

Ozonolysis of Isodrimene.—Isodrimene (29 mg.) in dry methylene chloride (15 ml.) was treated with ozonised oxygen at −60° until a test was negative to tetranitromethane and the solution was blue (20 min.). Decomposition of the ozonide with zinc in acetic acid followed by chromatography over activated alumina (grade III) afforded the nor-ketone.

Drimanol and 8α-Drimanol.—Drimenol (1·0 g.) was hydrogenated in "AnalaR" ethyl acetate (100 ml.) with Adams catalyst (200 mg.) at 20°/1 atm. The theoretical amount of hydrogen was absorbed in 20 min. Filtration and removal of solvent afforded *drimanol* (needles from aqueous acetone; 712 mg.), m. p. 110—111°, $[\alpha]_D$ +15° (*c* 4·27 in benzene) (Found: C, 80·4; H, 12·65. $C_{15}H_{28}O$ requires C, 80·3; H, 12·6%).

Attempts to separate 8α-drimanol from the hydrogenation product by chromatography over activated alumina (grade III) were only partly successful, 8α-drimanol being obtained pure from the head fractions in small yield.

A separation was achieved from two successive chromatograms of the mixed 3,5-dinitrobenzoates on activad tealumina (grade III), followed by fractional crystallisation from alcohol.

Obtained in this way, 8α-drimanyl 3,5-dinitrobenzoate crystallised from aqueous alcohol in needles, m. p. 103—104° (Found: C, 63·35; H, 7·55. $C_{22}H_{30}O_6N_2$ requires C, 63·15; H, 7·25%). The dinitrobenzoate was hydrolysed by heating it (13 mg.) in dioxan (0·5 ml.) and 10% methanolic potassium hydroxide (0·5 ml.) on the steam-bath for 1·5 hr. *8α-Drimanol* (7 mg.) was obtained by dilution, centrifugation, and sublimation at 10^{-3} mm., the initially colourless oil crystallising in needles, m. p. 60—62°, $[\alpha]_D$ +4° (*c* 1·16 in benzene) (Found: C, 80·0; H, 12·2. $C_{15}H_{28}O$ requires C, 80·3; H, 12·6%). *Drimanyl 3,5-dinitrobenzoate*, obtained during this separation from chloroform–ethanol in long plates, had m. p. 139—140° (Found: C, 63·05; H, 7·5; N, 6·75. $C_{22}H_{30}O_6N_2$ requires C, 63·15; H, 7·25; N, 6·7%). Hydrolysed as for 8α-drimanyl 3,5-dinitrobenzoate, it afforded drimanol, m. p. alone and mixed with material direct from the hydrogenation 110—111°.

Drimanyl α-Naphthylurethane.—Drimanol (100 mg.), α-naphthyl isocyanate (100 mg., 1·3 mol.), and light petroleum (b. p. 100—120°; 3 ml.) were kept at 120° during 45 min. Dilution with light petroleum (b. p. 100—120°; 2 ml.) and cooling afforded the *α-naphthylurethane* in needles [(from light petroleum (b. p. 100—120°)], m. p. 157—159° (Found: C, 79·6; H, 9·4. $C_{26}H_{35}O_2N$ requires C, 79·35; H, 8·95%).

Drimenyl α-Naphthylurethane.—Drimenol (100 mg.) similarly afforded its *α-naphthylurethane* in prisms [from light petroleum (b. p. 100—120°)], m. p. 110—112° (Found: C, 79·8; H, 8·55. $C_{26}H_{33}O_2N$ requires C, 79·75; H, 8·5%).

Drimanyl Toluene-p-sulphonate.—Drumanol (225 mg.) and freshly crystallised toluene-*p*-sulphonyl chloride (380 mg., 2 mol.) were kept in " AnalaR " pyridine (4 ml.) for 16 hr. at room temperature. The suspension of pyridine hydrochloride was poured into ice-cold saturated aqueous sodium carbonate. After 1 hr., ether-extraction and working-up in the usual way afforded the *drimanyl ester* (154 mg.) in needles [from light petroleum (b. p. 60—80°)], m. p. 95—97°, raised by one further crystallisation to 104—105°, $\lambda_{max.}$ 225 mμ (ε 13,000) (Found: C, 70·1; H, 9·05. $C_{22}H_{34}O_3S$ requires C, 69·8; H, 9·05%).

Driman-11-oic Acid.—To drimanol (400 mg.) in " AnalaR " acetic acid (5 ml.) was added dropwise a solution of chromic anhydride (130 mg. = 2·2 O) in 80% acetic acid (5 ml.) containing potassium hydrogen sulphate (130 mg.). After 1 hr. dilution with water, ether-extraction, etc., and removal of solvents under reduced pressure left a pale green oil which partly crystallised and had $\nu_{max.}$ (Nujol mull) 1700 (CO_2H), 3400—2390 (associated OH of CO_2H), and 1735 $cm.^{-1}$ (aldehyde).

This acid–aldehyde mixture in ethanol (15 ml.) was added dropwise and with stirring to a freshly prepared suspension of silver oxide (from 575 mg. of silver nitrate) on the steam-bath, and heated for an hour. Dilution with hot water (10 ml.), filtration, acidification, and ether-extraction, afforded a pale yellow oil from which driman-11-oic acid crystallised spontaneously as prisms (from aqueous ethanol), $[\alpha]_D$ (in chloroform) +14° (*c* 1·70), m. p. and mixed m. p. 135—136° (cf. ref. 7) (Found: C, 75·3; H, 11·1. Calc. for $C_{15}H_{26}O_2$: C, 75·6; H, 11·0%). The methyl ester formed needles (from aqueous ethanol), m. p. 49—50° (Ruzicka *et al.*[7] give m. p. 50—50·5°).

Nordrimenone.—(*a*) To drimenol (2·2 g.) in " AnalaR " acetone (15 ml.) was added dropwise and with stirring chromic anhydride (2·35 g., 3·5 O) and potassium hydrogen sulphate (2·35 g.) in 5 : 4 aqueous acetic acid (45 ml.). After 1 hr., the excess of oxidant was decomposed with methanol, most of the solvent removed at 40°, and the residue diluted with water, ether-extracted, and separated into neutral (1·89 g.) and acid (not further examined) fractions. Adsorption of the neutral fraction from benzene–light petroleum (1 : 2) on activated alumina (60 g.; grade III) and elution with the same solvent afforded nordrimenone (590 mg.) as needles. From aqueous ethanol it formed rods, m. p. 84—85°, $[\alpha]_D$ −67° (*c* 1·59 in benzene), $\lambda_{max.}$ 235 mμ (ε 6500), $\nu_{max.}$ (in chloroform) 1670 (αβ-unsaturated cyclohexanone) $cm.^{-1}$ (Found: C, 81·35; H, 10·55. Calc. for $C_{14}H_{22}O$: C, 81·50; H, 10·75%). Elution with solvent mixtures of increasing polarity gave only oils which were not further investigated.

(*b*) To drimenol (10·0 g.) in " AnalaR " acetic acid (150 ml.) was added dropwise and with stirring Beckmann's mixture (147 ml.); the rate of addition of the first 50 ml. was regulated to keep the temperature below 40°. Stirring was continued for 1 hr. more and the mixture kept at 20° for 4 days. Addition of water (500 ml.) resulted in the separation of crude nordrimenone (6—6·5 g.), which was washed with water. A further 1—1·5 g. were obtained from the mother-liquors.

Drimic Acid.—(*a*) Nordrimenone (528 mg.) in " AnalaR " acetic acid (20 ml.) was treated

dropwise and with stirring with sodium dichromate (1·56 g., 6 O) in sulphuric acid (1·1 ml.) and water (8·9 ml.). The mixture was kept for 0·5 hr. at 20°, then 0·5 hr. at 40°. Dilution with water, ether-extraction, removal of sulphuric acid by extraction with four-fifths saturated aqueous sodium chloride, extraction of the acid into 1·5N-sodium hydroxide, acidification, and re-extraction into ether afforded drimic acid (123 mg.), prisms (from acetone–light petroleum), m. p. 167—168° alone or mixed with an authentic specimen,[8] $[\alpha]_D$ −7° (*c* 4·62 in acetone) (Found: C, 63·15; H, 9·1. Calc. for $C_{12}H_{20}O_4$: C, 63·15; H, 8·85%).

(*b*) Nordrimenone (325 mg.) in dry methylene chloride was treated with ozonised oxygen at −10° until a test sample did not show $\lambda_{max.}$ 237 mμ (10 min.). Water (20 ml.) was added, and the methylene chloride removed in a stream of nitrogen while the solution was gradually warmed to 60°. The acidic product (220 mg.) recovered in the usual way was adsorbed from benzene on chromatographic silica gel (15 g.). Benzene–ether (1 : 1) eluted an oil (153 mg.) which was sublimed (3×10^{-4} mm.) and afforded drimic acid (from acetone–light petroleum), m. p. alone and mixed with material prepared by method (*a*) 166—168°.

In another experiment with 330 mg. of nordrimenone, the volatile acid formed in the ozonolysis was distilled into an equivalent amount of 0·1N-sodium hydroxide, and the solution divided into halves. One was taken to dryness and the residue exhibited $\nu_{max.}$ (KCl disc) 1585 cm.$^{-1}$ (AcO) as did an authentic specimen prepared from acetic acid.

The other half was concentrated to 5 ml., just acidified to phenolphthalein with 0·1N-hydrochloric acid and refluxed for 1 hr. with *p*-bromophenacyl bromide (225 mg.) with the addition of ethanol to produce a clear solution. Ether-extraction and adsorption of the residue on activated alumina [10 g. grade (V)] from light petroleum gave, on elution with the same solvent, first *p*-bromophenacyl bromide (8 mg.) (m. p. and mixed m. p.), followed by an oily mixture (53 mg.), and then *p*-bromophenacyl acetate (60 mg.; m. p. and mixed m. p.). Rechromatography of the oily intermediate fractions afforded a further 23 mg. of *p*-bromophenacyl acetate (total 40%).

Determination of gem*-Dimethyl Groupings in Drimanol, 8α-Drimanol, and Isodrimanol by Measurement of Apparent Integrated Infrared Absorption Intensities* (β).—Spectra were recorded linearly in cm.$^{-1}$ as % transmission (kindly determined by Dr. G. Eglinton, Mr. F. Gisbey, and Mr. J. F. Morman) with a Unicam S.P. 100 double-beam infrared spectrometer equipped with an S.P. 130 sodium chloride prism–1500 line per inch grating double monochromator (vacuum). The wave-number scale was calibrated [28,29] against polystyrene, methane, and water vapour and has an absolute accuracy better than ±1 cm.$^{-1}$. The spectra were determined under conditions ensuring resolution of water-vapour bands similar to that recorded by Downie *et al.*[28] (CaF_2, double pass); a spectrum of cholestanol (in carbon tetrachloride) exhibited slightly better peak separation than that in the literature [30] but was otherwise identical both in appearance and the position of peaks.

The compounds were examined as solutions in " AnalaR " carbon tetrachloride in the same pair of 2 mm. cells, over the region 1300—1500 cm.$^{-1}$ at a scanning speed of 20 cm.$^{-1}$ per min., the zero % transmission being accurately set before and after each run. 8α-Drimanol, available in very small quantity, was examined only qualitatively in a 1 cm. cell.

The apparent integrated absorpt ionintensities [31] (β), where $\beta = \frac{1}{cl}\int \ln\left(\frac{T_0}{T}\right) d\nu$ and c = molar concn., l = cell path (cm.), were determined by measurement of optical densities every

Compound *	*gem*-Me_2 alone (symmetric)		All Me groups (symmetric)		CH_2 + Total Me (antisymmetric)	
	Range	$10^{-3}\beta$	Range	$10^{-3}\beta$	Range	$10^{-3}\beta$
Drimanol	1330—1375	2·11	1375—1420	4·22	1420←1485 †	7·37
Isodrimanol	1330—1378	3·67	1378—1420	2·73	1420—1485 †	6·50

β in l. mole^{-1} cm.$^{-2}$.

* Drimanol and isodrimanol were examined as 0·0248M- and 0·0291M-solution, respectively.

† Integration was not continued beyond 1485 cm.$^{-1}$ as the lack of spectrometer energy consequent upon the rapidly increasing solvent absorption might have resulted in decreased accuracy.

[28] Downie, Magoon, Purcell, and Crawford, *J. Opt. Soc. Amer.*, 1953, **43**, 941.
[29] Plyler, Blaine, and Nowak, *J. Res. Nat. Bur. Stand.*, 1957, **58**, 195.
[30] Dobriner, Katzenellenbogen, and Jones, " Atlas of Infra Red Absorption Spectra of Steroids," Vol. I, Interscience, Publ. Inc., New York, 1953.
[31] Jones and Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 80.

2 cm.$^{-1}$, followed by application of Simpson's rule.[32] For integration, 100% transmission was taken as that observed at 1420 cm.$^{-1}$.

We cordially thank Professor D. H. R. Barton, F.R.S., for valuable discussion, and Professor R. A. Raphael and Drs. J. Reid and E. Miller for their encouragement.

UNIVERSIDAD TECNICA FEDERICA SANTA MARIA, VALPARAISO, CHILE.
M.R.C. CLINICAL CHEMOTHERAPEUTIC RESEARCH UNIT, WESTERN INFIRMARY, GLASGOW.
CHEMISTRY DEPARTMENT, THE UNIVERSITY, GLASGOW. [*Received, April 7th*, 1959.]

[32] Handbook of Chemistry and Physics, 39th edn., p. 318, Chemical Rubber Publ. Co.

---

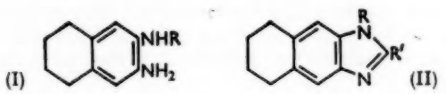
674. *Naphthimidazoles. Part II.*[1] 5,6,7,8-*Tetrahydronaphth*[2,3]-*imidazole and Some Derivatives.*

By D. J. BROWN and R. J. HARRISSON.

5,6,7,8-Tetrahydronaph[2,3]imidazole and some of its $C_{(2)}$-derivatives have been prepared. In their ionization constants and ultraviolet spectra they resemble the benzimidazoles more than the linear naphthimidazoles.

FOLLOWING a brief study of 2-substituted linear naphthimidazoles,[1] representative derivatives of the related 5,6,7,8-tetrahydronaphth[2,3]imidazole series have been made. Only one derivative (II; R = H; R′ = Me) has been previously described,[2] and the ultraviolet spectra and pK_a values of the new 2-substituted derivatives form a logical link between those of the benzimidazoles and naphthimidazoles.

6,7-Diaminotetralin (I; R = H) [2,3] was boiled with formic or propionic acid, the parent 5,6,7,8-tetrahydronaphth[2,3]imidazole (II; R = R′ = H) or 2-ethyl derivative being formed, respectively. Fusion of the diamine with urea gave 5,6,7,8-tetrahydro-2-hydroxynaphth[2,3]imidazole which (unlike its fully aromatic analogue [1]) was converted with phosphoryl chloride into the 2-chloro-derivative (II; R = H; R′ = Cl). The chlorine



(I) (II)

was readily replaced by an anilino-group and in poor yield by a dimethylamino-group. From ammonia, methylamine, or methanolic sodium methoxide, the chloro-compound was recovered, or under more severe conditions it was destroyed. However, the 2-amino-derivative was obtained directly from 6,7-diaminotetralin and cyanogen bromide although an attempt to make the 2-ethoxy-derivative with diethyl imidocarbonate (as 2-ethoxybenziminazole [4]) failed. The 2-mercapto-compound was obtained from thiourea and the diaminotetralin; methylation gave the 2-methylthio-derivative, and sodium chloroacetate the 2-carboxymethylthio-derivative, which on treatment with acetic anhydride cyclized by amide linkage on to $N_{(1)}$ giving the naphthothiazoloimidazole (II; RR′ = $CO{\cdot}CH_2{\cdot}S$).

Although the parent compound and its 2-mercapto-derivative could not be *N*-methylated satisfactorily, these compounds were obtained by direct synthesis from 2-amino-5,6,7,8-tetrahydro-3-methylaminonaphthalene [5] (I; R = Me) with, respectively, formic acid and thiourea.

[1] The paper by Brown, *J.*, 1958, 1974, is considered to be Part I of this series.
[2] Schroeter, *Annalen*, 1922, **426**, 17.
[3] Mayer and Schirmacher, D.R.P. 434,403; *Chem. Zentr.*, 1926, II, 2496.
[4] Sandmeyer, *Ber.*, 1884, **19**, 2650.
[5] Kuhn, Vetter, and Rzeppa, *Ber.*, 1937, **70**, 1302.

The transition from benzimidazole to linear naphthimidazole results [1] in a marked weakening of the basic strength, from pK_a 5·53 to pK_a 5·24. When the added ring is paraffinic as in 5,6,7,8-tetrahydronaphthimidazole, no such weakening occurs and the normal increase in basic strength associated with *C*-alkylation is seen in a pK_a of 5·98, comparable for example with that of 5,6-dimethylbenzimidazole (6·11). Further *C*-alkylation at $C_{(2)}$ again increases the basic strength as in 2-ethyl-5,6,7,8-tetrahydronaphthimidazole (pK_a 6·64). 2-Aminotetrahydronaphthimidazole is similarly a stronger base (7·69) than 2-aminonaphthimidazole (7·01). In acidic properties, tetrahydronaphthimidazole (pK_a 13·3) is almost identical with 5,6-dimethylbenzimidazole, and rather weaker than the fully aromatic linear naphthimidazole (12·5); similar relations apply for the 2-hydroxy- and 2-mercapto-derivatives.

The ultraviolet spectra in the Table indicate a closer resemblance of the tetrahydronaphthimidazoles to the benzimidazoles than to the linear naphthimidazoles. There is a slight bathochromic shift of the long wave length bands (cation and neutral molecule) between 5,6-dimethylbenzimidazole and tetrahydronaphthimidazole, but a very marked hypsochromic shift on approaching the latter from linear naphthimidazole. As in the naphthimidazoles, the spectra of the reduced hydroxy-derivative (anion) and the amino-derivative (neutral molecule) are almost identical, as are also those of the carboxymethyl thio-anion and of the corresponding methylthio-derivative. The spectra of the dimethylamino-compound bear the usual close resemblance to those of the parent amino-compound.

5,6,7,8-Tetrahydronaphth[2,3]imidazole derivative	pK_a (20°) [a] and concn. (10^{-5}M) in brackets	Ultraviolet spectra in water: pH	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$
Unsubst.	—	8·0	291; 282; 252	3·78; 3·78; 3·62
cation	5·98 (±0·02) [b] [100]	3·5	289; 279	3·86; 3·87
anion	13·33 (±0·02) [2·5]			
2-Ethyl-	—	9·5	293; 287; 283; 250	3·82; 3·86; 3·85; 3·65
cation	6·64 (±0·03) [2·5]	3·0	290; 281	3·91; 3·93
2-Hydroxy-	—	7·0	290	3·88
anion	12·21 (±0·03) [2·5]	14·0	298; 245 [f]	3·92; 3·65
di-anion	*ca.* 15·5			
2-Mercapto-	—	6·7	311; 303; 248	4·43; 4·36; 4·15
anion	10·43 (±0·05) [0·65]	12·5	310; 258	4·30; 3·96
2-Methylthio-	—	7·5	302; 294	4·20; 4·20
cation	*ca.* 5·0 [c] [0·625]	0	303; 296	4·30; 4·28
anion	*ca.* 13 [0·625]			
2-Chloro-	—	6·5	293; 283; 251	3·94; 3·94; 3·68
cation	2·68 (±0·05) [1·25]	0	294; 284	4·03; 4·06
2-Dimethylamino-	—	10	301; 248	4·10; 3·82
cation	7·65 (±0·01) [1·25]	4·5	293; 234 [g]	4·08; 3·93
anion	>13 [1·25]			
2-Carboxymethylthio-	—	3·1 [c]	303; 297	4·29; 4·27
anion	*ca.* 5·2 [c]	8·5	303; 295	4·20; 4·20
2-Amino-	—	10	293; 244	3·97; 3·76
cation	7·69 (±0·03) [1·25]	3·5	287	3·99
2-Mercapto-3-methyl-	—	6·5	312; 304 [f]; 244	4·42; 4·39; 4·29
anion	10·78 (±0·07) [0·625]	13·0	313; 263	4·35; 3·99
Other compounds				
Naphth[2,3]imidazole [d]	—		342; 327; 317; 235	3·74; 3·88; 3·83; 4·79
cation	5·24		325; 318; 235	3·90; 3·84; 4·75
anion	12·52			
5,6-Dimethylbenzimidazole [h]	—	8·0	286; 279; 277 [f]; 246	3·67; 3·66; 3·66; 3·59
cation	6·11 (±0·02) [b] [500]	3·5	283; 276 [f]; 274; 246	3·79; 3·77; 3·77; 3·41
anion	12·52			

[a] Most values spectroscopically determined. [b] Potentiometrically determined. [c] The densities of species are too close for an accurate pK_a determination. [d] Figures from ref. 1. [e] Probably contaminated with cation; cationic pK_a unobtainable. [f] Inflexion. [g] Plateau. [h] Prepn.: ref. 7.

[6] Crippa and Maffei, *Gazzetta*, 1941, **71**, 418.
[7] Takatori, Yamada, and Kawashima, *J. Pharm. Soc. Japan*, 1955, **75**, 881.

Experimental

5,6,7,8-*Tetrahydronaphth*[2,3]*imidazole*.—6,7-Diaminotetralin [1,2] (1 g.) was refluxed with 98% formic acid (5 ml.). After 4 hr. the cooled solution was poured on ice and the pH adjusted to 7—8 by addition of sodium carbonate solution. Recrystallisation of the product (1 g.) from benzene (10 ml.) gave an adduct (m. p. 86—88°). The free *tetrahydronaphthimidazole*, m. p. 134—135°, was obtained by sublimation (130°/0·1 mm.) (Found: C, 76·5; H, 7·2; N, 16·2. $C_{11}H_{12}N_2$ requires C, 76·7; H, 7·0; N, 16·3%).

5,6,7,8-*Tetrahydro*-1-*methylnaphth*[2,3]*imidazole*.—6-Amino-7-methylaminotetralin [5] was treated with formic acid as above. The crude oily product was removed with ether and distilled giving the N-*methyl compound* as a pale yellow unstable oil, b. p. 180°/0·2 mm. It solidified at room temperature (Found: N, 15·0. $C_{12}H_{14}N_2$ requires N, 15·0%).

2-*Ethyl*-5,6,7,8-*tetrahydronaphth*[2,3]*imidazole*.—Prepared similarly to the parent compound, the *ethyl* analogue formed needles, m. p. 242—243° (from 50% ethanol, 30 parts) (Found: C, 77·9; H, 8·2; N, 13·95. $C_{13}H_{16}N_2$ requires C, 77·95; H, 8·05; N, 14·0%).

5,6,7,8-*Tetrahydro*-2-*hydroxynaphth*[2,3]*imidazole*.—An intimate mixture of 6,7-diaminotetralin (1 g.) and urea (1 g.) was heated under nitrogen at 160°. After 4 min. the mass solidified and after a further 5 min. it was cooled and water (10 ml.) added. The solid (1·15 g.) was recrystallised from ethanol (100 parts) to give the *hydroxy-derivative* as white laths, m. p. 355° (Found: C, 70·2; H, 6·5; N, 14·8. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·3; N, 14·9%).

5,6,7,8-*Tetrahydro*-2-*mercaptonaphth*[2,3]*imidazole*.—Fusion, as above, of the diaminotetralin and thiourea at 190° and recrystallisation from 70% ethanol (40 parts) gave the *mercapto-derivative* as needles, m. p. 310° (Found: C, 64·7; H, 6·0; N, 13·7. $C_{11}H_{12}N_2S$ requires C, 64·7; H, 5·9; N, 13·7%).

5,6,7,8-*Tetrahydro*-2-*mercapto*-1-*methylnaphth*[2,3]*imidazole*.—6-Amino-7-methylaminotetralin [5] (0·8 g.) and thiourea (0·8 g.) were heated under nitrogen at 200° for 15 min. Water (10 ml.) was added, and the solid (0·5 g.) treated with charcoal and recrystallised from ethanol (50 parts), giving the *mercapto-methylnaphthimidazole* as needles, m. p. 250—252° (Found: C, 66·0; H, 6·6; N, 13·0. $C_{12}H_{14}N_2S$ requires C, 66·0; H, 6·5; N, 12·8%).

5,6,7,8-*Tetrahydro*-2-*methylthionaphth*[2,3]*imidazole*.—The mercapto-derivative (0·8 g.) in 0·1N-sodium hydroxide (45 ml.; 10% excess) was shaken with dimethyl sulphate (0·55 g.) for 1 hr. at 25°. The pH of the solution was adjusted to *ca.* 5 and the solid filtered off. Recrystallisation from 50% aqueous propanol (30 parts) gave the *methylthio-compound* as needles, m. p. 195° (Found: C, 66·0; H, 6·5; N, 12·8. $C_{12}H_{14}N_2S$ requires C, 66·0; H, 6·5; N, 12·8%).

2-*Chloro*-5,6,7,8-*tetrahydronaphth*[2,3]*imidazole*.—2-Hydroxytetrahydronaphthimidazole (0·56 g.) and phosphoryl chloride (6 ml.) were refluxed for 6 hr. Volatile material was partially removed *in vacuo* and the residue poured on ice (20 g.). A little insoluble material was filtered off and the pH of the filtrate adjusted to *ca.* 7 with dilute ammonia solution. The precipitate (0·4 g.) was recrystallised from 50% aqueous ethanol (40 parts) giving the *chloro-compound*, m. p. 211° (Found: C, 64·0; H, 5·4; N, 13·55. $C_{11}H_{11}N_2Cl$ requires C, 63·9; H, 5·4; N, 13·55%)

2-*Anilino*-5,6,7,8-*tetrahydronaphth*[2,3]*imidazole*.—The 2-chloro-derivative (0·5 g.) and aniline (5 ml.) were refluxed under nitrogen for 2·5 hr. Steam-distillation removed excess of aniline, and the crystalline residue (0·5 g.) was washed with dilute ammonia solution, recrystallised from isobutyl methyl ketone (30 parts), and sublimed in a vacuum to give the *anilino-compound*, m. p. 247—249° (Found: C, 77·3; H, 6·4. $C_{17}H_{17}N_3$ requires C, 77·5; H, 6·5%).

2-*Dimethylamino*-5,6,7,8-*tetrahydronaphth*[2,3]*imidazole*.—The 2-chloro-derivative (0·35 g.) and aqueous dimethylamine (30%; 10 ml.) were heated at 150° for 3 hr. The pH was adjusted to *ca.* 1, and the solution treated with charcoal. Adjustment of the pH of the filtrate to 8 gave a crude product (0·2 g.) which was crystallised, sublimed in a vacuum, and recrystallised from benzene (100 parts) to give the *dimethylamino-derivative*, m. p. 210—211° (Found: C, 72·3; H, 7·9. $C_{13}H_{17}N_3$ requires C, 72·5; H, 7·95%).

2-*Carboxymethylthio*-5,6,7,8-*tetrahydronaphth*[2,3]*imidazole*. — Tetrahydro-2-mercaptonaphthimidazole (1·43 g.) in N-sodium hydroxide (7 ml.) was heated at 100° with chloroacetic acid (0·7 g.) in 2·5N-sodium hydroxide (3 ml.) for 2 hr. The solution was cooled and diluted with water (10 ml.), and the pH adjusted to 2—3. Recrystallisation from ethanol (100 parts) gave the *acid* as needles, m. p. 194—195° (1·8 g.) (Found: C, 59·5; H, 5·4; N, 10·5. $C_{13}H_{14}SO_2N_2$ requires C, 59·5; H, 5·4; N, 10·7%).

1,2,6,7,8,9-*Hexahydro*-1-*oxonaphtho*[2,3-*d*]*thiazolo*[3,2-*a*]*imidazole*.—The above acid (0·7 g.) and pyridine (3 ml.) were heated on the steam-bath with acetic anhydride (1 ml.) for 15 min., and the mixture then cooled and diluted with water (25 ml.). The solid was extracted with boiling ethanol (25 ml.), and the extract concentrated to 15 ml., diluted with water (15 ml.), and cooled. The needles of *naphthothiazoloimidazole* had m. p. 161° (Found: C, 63·8; H, 5·0; N, 14·5. $C_{13}H_{12}ON_2S$ requires C, 63·9; H, 4·95; N, 14·5%).

2-*Amino*-5,6,7,8-*tetrahydronaphth*[2,3]*imidazole*.—Cyanogen bromide [6] [from the addition of potassium cyanide (0·63 g.) in water (3 ml.) to bromine (1·45 g.) at 0°] in cold water (15 ml.) was added to a stirred suspension of 6,7-diaminotetralin (1·4 g.). Next morning the oily mixture was diluted with water and made alkaline, and the solid filtered off. After three sublimations *in vacuo*, the *amine* (1·35 g.) had m. p. 220° (Found: C, 70·75; H, 7·15; N, 22·35. $C_{11}H_{13}N_3$ requires C, 70·6; H, 7·0; N, 22·4%).

We thank Mr. F. Robinson for the physical measurements and Dr. J. E. Fildes and her staff for the analyses.

Department of Medical Chemistry,
Australian National University, Canberra. [*Received, April 28th*, 1959.]

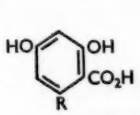
---

675. *Lactones. Part VI.* The Preparation of 5,7-Dihydroxyphthalide, its 5-Methyl Ether, and Related Compounds.*

By W. R. Allison and G. T. Newbold.

Ethyl dibromo-orsellinate has been converted into 5,7-dihydroxyphthalide by successive photobromination, hydrolysis, and hydrogenolysis; and ethyl everninate has been similarly transformed into 7-hydroxy-5-methoxyphthalide.

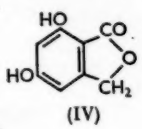
This investigation was initiated in order to find a suitable synthesis of 5,7-dihydroxyphthalide (IV) which might be a useful intermediate for synthesis of the acids (I) and (II) [1] elaborated by *Penicillium brevi-compactum*. 5,7-Dihydroxyphthalide could be postulated as a possible intermediate along with orsellinic acid (III) in the biosynthesis of variolaric acid [2] (V), a constituent of the lichen *Lecanora parella* Ach. 7-Hydroxy-5-methoxyphthalide (XIV) was also desired since it might serve as an intermediate for the synthesis of mycophenolic acid [3,4] (VI).



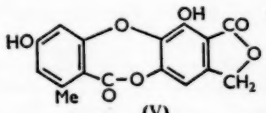
(I) R = CH(OH)·COMe

(II) R = CO·COMe, H_2O

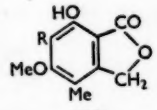
(III) R = Me



(IV)



(V)



(VI)

R = CH_2·CH:CMe·$[CH_2]_2$·CO_2H

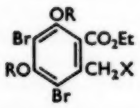
5,7-Dihydroxyphthalide has been prepared starting from ethyl dibromo-orsellinate [5] (VII). Photobromination of this ester gave in almost quantitative yield the tribromo-ester (VIII) which on hydrolysis in aqueous dioxan yielded 4,6-dibromo-5,7-dihydroxyphthalide (XI), characterised as its diacetate (XII)—the usual alkaline hydrolysis

* Part V, *J.*, 1957, 1946.

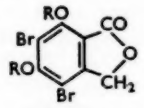
[1] Clutterbuck, Oxford, Raistrick, and Smith, *Biochem. J.*, 1932, **26**, 1441; Oxford and Raistrick, *ibid.*, p. 1902; 1933, **27**, 634, 1473.
[2] Murphy, Keane, and Nolan, *Sci. Proc. Roy. Dublin Soc.*, 1943, **23**, 71.
[3] Birkinshaw, Raistrick, and Ross, *Biochem. J.*, 1952, **50**, 630.
[4] Logan and Newbold, *J.*, 1957, 1946.
[5] Cf. Sonn, *Ber.*, 1928, **61**, 926.

XUM

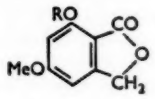
technique [4,6] was not successful. 4,6-Dibromo-5,7-dihydroxyphthalide was not hydrogenolysed to 5,7-dihydroxyphthalide (IV) by the method [4] used to convert 4-bromo-5,7-dimethoxyphthalide (XVIII) into 5,7-dimethoxyphthalide (XV), but use of palladium on calcium carbonate in the presence of alkali [5] was successful.



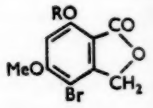
(VII) R = X = H
(VIII) R = H, X = Br
(IX) R = Me, X = Br
(X) R = Me, X = H



(XI) R = H
(XII) R = Ac
(XIII) R = Me



(XIV) R = H
(XV) R = Me

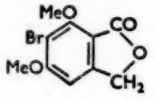


(XVI) R = H
(XVII) R = Ac
(XVIII) R = Me

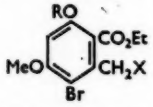
With diazomethane 5,7-dihydroxyphthalide rapidly gave 5,7-dimethoxyphthalide (XV). Ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (VIII) gave an oil which from its reactions described below must have been the ether (IX); ethyl dibromo-orsellinate (VII) was similarly converted into the ether (X). These methylations contrast with the action of diazomethane on ethyl orsellinate which under these conditions gave ethyl everninate (XXIV), only the 4-hydroxyl group having reacted.[7] Clearly the enhanced acidity of the 6-hydroxy-group in (VII) and (VIII), due to the ring deactivation of the bromine atoms, overcomes the lack of reactivity of the hydroxyl group due to hydrogen-bonding with the ester-carbonyl group.

The crude ethyl 3,5-dibromo-2-bromomethyl-4,6-dimethoxybenzoate (IX), to which reference was made above, was hydrolysed in aqueous dioxan to 4,6-dibromo-5,7-dimethoxyphthalide (XIII); this was also prepared from the phthalide (XI) by means of diazomethane. Replacement of both bromine atoms in the phthalide (XIII) by hydrogen, giving 5,7-dimethoxyphthalide (XV), was effected catalytically in aqueous alkali; on hydrogenolysis with palladium–charcoal in ethyl acetate, the product was 6-bromo-5,7-dimethoxyphthalide (XIX) even after prolonged treatment, and this was fully debrominated by hydrogenolysis in aqueous alkali in the presence of palladium–calcium carbonate.

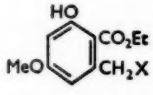
The starting material for the synthesis of 7-hydroxy-5-methoxyphthalide (XIV) was ethyl everninate [7] (XXIV). Photobromination of the ester with 1 mol. of bromine in presence of a little methanol gave mainly ethyl 3-bromo-6-hydroxy-4-methoxy-2-methylbenzoate (XX) [identified as the dimethoxy-ester (XXI) which was also prepared by



(XIX)



(XX) R = X = H
(XXI) R = Me, X = H
(XXII) R = H, X = Br
(XXIII) R = Me, X = Br



(XXIV) X = H
(XXV) X = Br

esterification of the known 4,6-dimethoxy-acid [4]], but in the absence of methanol ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate (XXV) was obtained in good yield. This was smoothly hydrolysed to 7-hydroxy-5-methoxyphthalide (XIV) in aqueous dioxan. A small amount of the bromomethyl compound (XXV) was isolated after photobromination in the presence of methanol. Photobromination of ethyl everninate with 2 mol. of bromine gave both nuclear and side-chain bromination: the product, (XXII), on hydrolysis in aqueous sodium carbonate or, better, aqueous dioxan afforded the bromophthalide (XVI).

[6] Eliel, Rivard, and Burgstahler, *J. Org. Chem.*, 1953, **18**, 1679.
[7] Fischer and Hoesch, *Annalen*, 1912, **391**, 347.

The last compound, which was characterised as its acetate (XVII), was readily hydrogenolysed to 7-hydroxy-5-methoxyphthalide (XIV). Ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (XXII) was rapidly methylated by diazomethane to give the dimethoxy-ester (XXIII) which on hydrolysis gave the known [4] 4-bromo-5,7-dimethoxyphthalide (XVIII). Both 7-hydroxy-5-methoxyphthalide and its 4-bromo-derivative reacted readily with diazomethane with the respective formation of the diethers (XV) and (XVIII).

The ready methylation of all the 7-hydroxyphthalides prepared in this work indicated the expected weakness of the intramolecular hydrogen bond between the carbonyl and the 7-hydroxyl group.[8] The same conclusion was drawn from the infrared spectra of the 7-hydroxyphthalides which showed carbonyl stretching frequencies in the range 1748—1732 cm.$^{-1}$ in chloroform (cf. 7-hydroxyphthalide,[9] 1738 cm.$^{-1}$). While 5,7-dimethoxyphthalide and its 4- and 6-bromo-derivative showed the predicted carbonyl peak at 1764—1761 cm.$^{-1}$ in chloroform (cf. phthalide 1761 cm.$^{-1}$), the 4,6-dibromo-derivative had its peak at 1776 cm.$^{-1}$ in this solvent (1770 cm.$^{-1}$ in Nujol and 1789 cm.$^{-1}$ in carbon tetrachloride); this effect cannot be ascribed to steric factors but may be due to the combined electron-attractive effect of both bromine substituents on their carbonyl group.[10] The effect of structural changes on their ultraviolet spectra in some of the compounds described above has been examined, the maximum (290—335 mμ) nearest the visible region being considered. As a consequence of the weak intramolecular hydrogen bond in the 7-hydroxyphthalides no appreciable shift occurs in this maximum on methylation [8] of the following: 4,6-dibromo-5,7-dihydroxy- Δ(mμ)—2, 5,7-dihydroxy- Δ 0, 4-bromo-7-hydroxy-5-methoxy- Δ—1·5, and 7-hydroxy-5-methoxy-phthalide Δ—1 (data from ref. 4 and this paper). The introduction of a bromo-substituent into the nuclear methyl group in the esters gave a bathochromic shift, thus: (XXI) ⟶ (XXIII) Δ 20, for the corresponding methyl esters [4] Δ 17·5, (VII) ⟶ (VIII) Δ 18, (XXIV) ⟶ (XXV) Δ 11, (XX) ⟶ (XXII) Δ 13. For a 3-bromo-substituent in ethyl everninate [(XXIV) ⟶ (XX)] Δ 8, and for the same change with ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate [(XXV) ⟶ (XXII)] Δ 10; hence a nuclear bromine atom gave a smaller bathochromic shift than if it had entered the side chain.

Experimental

Ultraviolet absorption spectra were determined for ethanol solutions. Brominations were in boiling dry carbon tetrachloride in a quartz flask mounted immediately above a 150 w lamp which both heated and irradiated the mixture.

Ethyl 3,5-*Dibromo*-4,6-*dimethoxy*-2-*methylbenzoate* (with J. Highet).—Ethyl dibromo-orsellinate, $\lambda_{max.}$ 224 (ε 28,500), 269 (ε 8500), and 317 mμ (ε 8500) (570 mg.), in methanol (5 c.c.) was treated with excess of ethereal diazomethane. After 2½ hr. evaporation and crystallisation from light petroleum (b. p. 60—80°) gave the *dimethoxy-ester* (610 mg., 98%) as prisms, m. p. 77—78° (Found: C, 38·0; H, 3·8. $C_{12}H_{14}O_4Br_2$ requires C, 37·7; H, 3·7%), $\lambda_{max.}$ 212 (ε 36,000) and 285 mμ (ε 700), $\nu_{max.}$ 1715 (in Nujol), 1727 cm.$^{-1}$ (in chloroform) (ester C=O).

Ethyl 3,5-*Dibromo*-2-*bromomethyl*-4,6-*dihydroxybenzoate* (with J. Highet).—To ethyl 3,5-dibromo-4,6-dihydroxy-2-methylbenzoate [5] (10 g.) in refluxing carbon tetrachloride (150 c.c.) was added during 30 min. bromine (4·52 g., 1 mol.) in carbon tetrachloride (20 c.c.). Refluxing was continued for a further 10 min., then the solvent was removed under reduced pressure. The residue crystallised from light petroleum (b. p. 60—80°) to give *ethyl* 3,5-*dibromo*-2-*bromomethyl*-4,6-*dihydroxybenzoate* (11·7 g.) as stout needles, m. p. 122—123° (Found: C, 28·1; H, 2·3. $C_{10}H_9O_4Br_3$ requires C, 27·7; H, 2·1%), $\lambda_{max.}$ 207 (ε 10,700), 234 (ε 15,800), 268 (ε 9000), and 335 mμ (ε 6400), $\nu_{max.}$ 1647 (in Nujol), 1667 cm.$^{-1}$ (in chloroform) (H-bonded ester). The compound in ethanol solution gave a deep purple colour with aqueous ferric chloride.

4,6-*Dibromo*-5,7-*dihydroxyphthalide*.—(*a*) (with J. Highet). A solution of ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (1·36 g.) in 10% aqueous sodium carbonate

[8] Farmer, Hayes, and Thomson, *J.*, 1956, 3600.
[9] Duncanson, Grove, and Zealley, *J.*, 1953, 1331.
[10] Cf. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1958, p. 391.

(136 c.c.) was heated for 1 hr. on the steam-bath, rapidly becoming dark brown. The cooled solution was acidified (Congo-red) with hydrochloric acid (*d* 1·15) and extracted with chloroform (3 × 20 c.c.). The combined chloroform extracts were washed with saturated aqueous sodium hydrogen carbonate (3 × 20 c.c.), and the alkaline washings were acidified (Congo-red) with hydrochloric acid (*d* 1·15). The solution was then extracted with chloroform (6 × 15 c.c.), and these extracts were dried (Na_2SO_4) and evaporated under reduced pressure to a brown solid. Crystallisation from chloroform gave 4,6-*dibromo*-5,7-*dihydroxyphthalide* (100 mg., 10%) as prisms, m. p. 236—238° (decomp.) (Found: C, 29·8; H, 1·4. $C_8H_4O_4Br_2$ requires C, 29·7; H, 1·3%), $\lambda_{max.}$ 224 (ε 38,100) and 304 (ε 9400), inflexion at 212 mμ (ε 14,000), $\nu_{max.}$ 1715 (in Nujol), 1748 cm.$^{-1}$ (in chloroform) (H-bonded phthalide C=O). An ethanolic solution of the compound gave a deep purple colour with aqueous ferric chloride.

(*b*) Ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (1·0 g.) was refluxed in dioxan (20 c.c.) and water (20 c.c.) for 24 hr. The dioxan was largely evaporated under reduced pressure, the residual aqueous solution allowed to crystallise, and the solid separated and dried. Recrystallisation from chloroform gave 4,6-dibromo-5,7-dihydroxyphthalide (680 mg., 91%) as prisms, m. p. and mixed m. p. 236—238° (decomp.). The identity of the phthalide preparation (*b*) with that of (*a*) was confirmed by comparison of infrared spectra in Nujol mull. Hydrolysis of ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate for 6 hr. with boiling 40% aqueous methanol, aqueous ethanol, absolute methanol, and absolute ethanol gave respectively 24, 55, 20, and 45% yields of the dibromophthalide.

The *diacetate*, prepared by the acetic anhydride–pyridine method, separated from methanol as plates, m. p. 162·5—164·5° (Found: C, 35·6; H, 2·1. $C_{12}H_8O_6Br_2$ requires C, 35·3; H, 2·0%), $\lambda_{max.}$ 217 (ε 41,500) and 296 mμ (ε 2600), $\nu_{max.}$ (in Nujol) 1775 (" phenolic " OAc) and 1751 (phthalide C=O), or (in chloroform) 1779 cm.$^{-1}$.

4,6-*Dibromo*-5,7-*dimethoxyphthalide*.—(*a*) A solution of 4,6-dibromo-5,7-dihydroxyphthalide (1·0 g.) in methanol (40 c.c.) was treated for 1 hr. with an excess of ethereal diazomethane. The solute crystallised from chloroform–methanol to give 4,6-*dibromo*-5,7-*dimethoxyphthalide* (1·02 g.) as needles, m. p. 136·5—138·5° (Found: C, 33·9; H, 2·4. $C_{10}H_8O_4Br_2$ requires C, 34·1; H, 2·3%), $\lambda_{max.}$ 222 (ε 40,200) and 302 mμ (ε 2400).

(*b*) A solution of ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (700 mg.) in methanol (1 c.c.) and ether (10 c.c.) was treated with an excess of ethereal diazomethane for 4 hr. A sample, on evaporation and dissolution in ethanol, then gave no colour with aqueous ferric chloride. Removal of the solvents gave an oil (725 mg.) [$\nu_{max.}$ (liquid) 1721 cm.$^{-1}$ (ester C=O)]; 350 mg. of this were dissolved in dioxan (20 c.c.), water (10 c.c.) was added, and the solution was refluxed for 24 hr. The dioxan was largely removed under reduced pressure, the aqueous solution cooled, and the separated solid filtered off and dried. Crystallisation from chloroform–methanol gave 4,6-dibromo-5,7-dimethoxyphthalide (244 mg., 85%) as felted needles, m. p. and mixed m. p. 136—138·5°. The infrared spectra of preparations (*a*) and (*b*) in Nujol were identical.

6-*Bromo*-5,7-*dimethoxyphthalide*.—A solution of 4,6-dibromo-5,7-dimethoxyphthalide (200 mg.) in dry ethyl acetate (50 c.c.) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of palladised charcoal (200 mg.; 2·5% of dichloride) and magnesium oxide (400 mg.). When absorption of hydrogen was complete (*ca.* 20 hr.) the mixture was filtered and the insoluble residue extracted with boiling chloroform (100 c.c.). The combined filtrates were evaporated under reduced pressure, and the residue crystallised from chloroform–methanol to give 6-*bromo*-5,7-*dimethoxyphthalide* (70 mg.) as blades, m. p. 207—209° (Found: C, 44·0; H, 3·3. $C_{10}H_9O_4Br$ requires C, 44·0; H, 3·3%); $\lambda_{max.}$ 219 (ε 32,900) and 257 (ε 12,200), inflexion at 287 mμ (ε 1500), $\nu_{max.}$ 1736 (in Nujol), 1764 cm.$^{-1}$ (in chloroform) (phthalide C=O). A mixed m. p. with 4-bromo-5,7-dimethoxyphthalide (lit.,[4] m. p. 246—248°) was 180—200°. The same yield of 6-bromo-5,7-dimethoxyphthalide was obtained when the dibromophthalide was hydrogenated under the same conditions but for 48 hr.

5,7-*Dihydroxyphthalide*.—4,6-Dibromo-5,7-dihydroxyphthalide (500 mg.) was shaken in 2N-aqueous sodium hydroxide (10 c.c.) with hydrogen at room temperature and atmospheric pressure in the presence of palladised calcium carbonate (1·0 g.; 2% of palladium hydroxide [11]). When absorption of hydrogen was complete (*ca.* 30 min.) the mixture was filtered and the filtrate acidified (Congo-red) with hydrochloric acid (*d* 1·15). The solid which slowly separated was filtered off, washed with a little water, and crystallised from aqueous methanol to give

[11] Busch and Stöve, *Ber.*, 1916, **49**, 1063.

5,7-dihydroxyphthalide (200 mg., 80%) as blades, m. p. 253—260° (decomp.), darkening at 235°, m. p. 257—260° *in vacuo* (Found: C, 57·7; H, 3·8. $C_8H_6O_4$ requires C, 57·8; H, 3·6%), $\lambda_{max.}$ 216 (ε 35,300), 255 (ε 15,000), and 290 mμ (ε 5000); $\nu_{max.}$ 1724 (in Nujol), 1732 cm.$^{-1}$ (in chloroform) (H-bonded phthalide C=O). A solution of the compound in ethanol gave a reddish-purple colour with aqueous ferric chloride.

Ethyl 3-Bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate.—To a refluxing solution of ethyl everninate,[7] $\lambda_{max.}$ 216 (ε 25,000), 263 (ε 15,000), and 301 mμ (ε 6000) (5·0 g.), in carbon tetrachloride (75 c.c.) bromine (7·61 g., 2 mols.) in carbon tetrachloride (20 c.c.) was added dropwise at such a rate that the colour due to the previous addition had virtually disappeared. Approximately 6 hr. were required; the solution was then refluxed for a further 30 min. The solvent was evaporated under reduced pressure, and the residue crystallised from light petroleum (b. p. 60—80°) to give *ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate* (5·3 g.) as needles, m. p. 103·5—105° (Found: C, 35·8; H, 3·4. $C_{11}H_{12}O_4Br_2$ requires C, 35·9; H, 3·3%), $\lambda_{max.}$ 228 (ε 28,600) and 322 (ε 5800), inflexions 209 (ε 15,200) and 264 mμ (ε 7100), $\nu_{max.}$ 1639 (in Nujol), $\nu_{max.}$ 1661 cm.$^{-1}$ (in chloroform) (H-bonded ester C=O). It gave a reddish-purple colour with ferric chloride (cf. above).

Ethyl 3-Bromo-2-bromomethyl-4,6-dimethoxybenzoate.—A solution of ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (1·0 g.) in methanol (20 c.c.) was treated with excess of ethereal diazomethane for 4 hr., whereafter it gave no ferric chloride colour. Evaporation and crystallisation from light petroleum (b. p. 40—60°) gave *ethyl 3-bromo-2-bromomethyl-4,6-dimethoxybenzoate* (880 mg.) as prisms, m. p. 98—100° (Found: C, 37·5; H, 3·8. $C_{12}H_{14}O_4Br_2$ requires C, 37·7; H, 3·7%), $\lambda_{max.}$ 221 (ε 25,400) and 308 mμ (ε 4100), $\nu_{max.}$ 1733 (in Nujol), 1724 cm.$^{-1}$ (in chloroform) (ester C=O). A solution of the ester (500 mg.) in dioxan (20 c.c.) and water (10 c.c.) was refluxed for 24 hr. Concentration of the solution, cooling, separation of the crystals, and recrystallisation from chloroform–methanol gave 4-bromo-5,7-dimethoxyphthalide (89%) as needles, m. p. and mixed m. p. 246—248° (lit.,[4] m. p. 246—248°). The infrared spectra of the two samples in Nujol were identical: $\nu_{max.}$ 1767 (in Nujol), 1763 cm.$^{-1}$ (in chloroform) (phthalide C=O).

4-Bromo-7-hydroxy-5-methoxyphthalide.—(*a*) Water (40 c.c.) was added to a solution of ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (1·8 g.) in dioxan (60 c.c.) and the solution refluxed for 24 hr. Concentration under reduced pressure gave a mainly aqueous solution which deposited solid on cooling. Crystallisation of the solid from chloroform gave *4-bromo-7-hydroxy-5-methoxyphthalide* (1·1 g., 88%) as prisms, m. p. 236—238° (decomp.) (Found: C, 41·6; H, 2·85; Br, 30·7. $C_9H_7O_4Br$ requires C, 41·7; H, 2·7; Br, 30·9%), $\lambda_{max.}$ 220 (ε 34,000), 247 (ε 10,100), and 300 mμ (ε 4200), $\nu_{max.}$ 1733 (in Nujol), $\nu_{max.}$ 1742 cm.$^{-1}$ (in chloroform (H-bonded phthalide C=O). It gave a purple colour with ferric chloride (cf. above).

(*b*) Ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (500 mg.) was heated in 10% aqueous sodium carbonate (50 c.c.) for 1 hr. on the steam-bath. The solution was cooled, acidified (Congo-red) with hydrochloric acid (*d* 1·15), and extracted continuously with boiling chloroform for 2 hr. The chloroform extract was washed with a little water, dried (Na_2SO_4), and evaporated. Crystallisation of the residue from chloroform gave 4-bromo-7-hydroxy-5-methoxyphthalide (170 mg., 50%) as prisms, m. p. and mixed m. p. 236—238° (decomp.). The infrared spectra of preparations (*a*) and (*b*) in Nujol mull were identical.

The *acetate*, prepared by the acetic anhydride–pyridine method, separated from methanol as plates, m. p. 164—166° (Found: C, 44·2; H, 3·3. $C_{11}H_9O_5Br$ requires C, 43·9; H, 3·0%), $\lambda_{max.}$ 219 (ε 36,700) and 260 mμ (ε 13,900), $\nu_{max.}$ 1779 (" phenolic " acetate C=O) and 1761 (phthalide C=O) (in Nujol) or 1786—1767 cm.$^{-1}$ (broad band) (in chloroform). 4-Bromo-7-hydroxy-5-methoxyphthalide in methanol with an excess of ethereal diazomethane for 1 hr. gave 4-bromo-5,7-dimethoxyphthalide (in good yield), separating from chloroform–methanol as needles, m. p. 246—248° alone or mixed with a specimen prepared by Logan and Newbold.[4] The infrared spectra of the two samples in Nujol were identical.

Ethyl 3-Bromo-6-hydroxy-4-methoxy-2-methylbenzoate.—Ethyl everninate (5·59 g.), which had been dried *in vacuo* at 60°, was dissolved in dry carbon tetrachloride (80 c.c.), and methanol (0·2 c.c.) was added. The refluxing solution was treated with bromine (4·26 g., 1 mol.) in carbon tetrachloride (25 c.c.) dropwise during 30 min. Refluxing was continued for 15 min., the solvent evaporated under reduced pressure, and the resulting yellow gum dissolved in hot light petroleum (b. p. 60—80°). Concentration of the solution and cooling gave crop A, and from similar treatment of the mother-liquor crop B was obtained (see next paragraph). Crop A, on

crystallisation from light petroleum (b. p. 60—80°), gave *ethyl* 3-*bromo*-6-*hydroxy*-4-*methoxy*-2-*methylbenzoate* (3·2 g.) as needles, m. p. 125—127° (Found: C, 45·7; H, 4·8. $C_{11}H_{13}O_4Br$ requires C, 45·7; H, 4·5%), $\lambda_{max.}$ 218 (ε 28,300), 262 (ε 8900), and 309 mμ (ε 4100), $\nu_{max.}$ 1650 (in Nujol), $\nu_{max.}$ 1655 cm.$^{-1}$ (in chloroform) (H-bonded ester). This gave a deep purple colour with ferric chloride (cf. above).

Ethyl 2-*Bromomethyl*-6-*hydroxy*-4-*methoxybenzoate*.—(*a*) A refluxing solution of dried ethyl everninate (2·0 g.) in carbon tetrachloride (30 c.c.) was treated with bromine (1·53 g., 1 mol.) in carbon tetrachloride (10 c.c.) during 30 min. After 15 minutes' further refluxing the solvent was evaporated under reduced pressure; the residue crystallised from light petroleum (b. p. 60—80°) to give *ethyl* 2-*bromomethyl*-6-*hydroxy*-4-*methoxybenzoate* (1·7 g.), as needles, m. p. 92—93·5° (Found: C, 45·8; H, 4·9. $C_{11}H_{13}O_4Br$ requires C, 45·7; H, 4·5%), $\lambda_{max.}$ 208 (ε 11,200), 224 (ε 17,700), 266 (ε 7100), and 312 mμ (ε 4900), $\nu_{max.}$ 1650 (in Nujol), $\nu_{max.}$ 1661 cm.$^{-1}$ (in chloroform) (H-bonded ester). It gave a pale reddish-brown colour with ferric chloride (cf. above).

(*b*) Crop B from the bromination of ethyl everninate in the presence of methanol recrystallised from light petroleum (b. p. 60—80°), to give ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate (0·6 g.) as needles, m. p. and mixed m. p. 92—93°. The preparations had identical infrared spectra in Nujol mull.

Ethyl 3-*Bromo*-4,6-*dimethoxy*-2-*methylbenzoate*.—(*a*) Ethyl 3-bromo-6-hydroxy-4-methoxy-2-methylbenzoate (250 mg.) in methanol (10 c.c.) with an excess of ethereal diazomethane (2 hr.) gave *ethyl* 3-*bromo*-4,6-*dimethoxy*-2-*methylbenzoate* (190 mg.), prisms [from light petroleum (b. p. 40—60°)], m. p. 83—84·5° (Found: C, 47·3; H, 4·85. $C_{12}H_{15}O_4Br$ requires C, 47·5; H, 5·0%), $\lambda_{max.}$ 207 (ε 35,400) and 288 mμ (ε 3300), $\nu_{max.}$ 1715 (in Nujol), $\nu_{max.}$ 1721 cm.$^{-1}$ (in chloroform) (ester C=O).

(*b*) 3-Bromo-4,6-dimethoxy-2-methylbenzoic acid [4] similarly gave prisms, m. p. 80—82° not depressed on admixture with preparation (*a*), which had the same infrared spectrum in Nujol mull.

7-*Hydroxy*-5-*methoxyphthalide*.—(*a*) 4-Bromo-7-hydroxy-5-methoxyphthalide (1·5 g.) was dissolved in warm 2N-aqueous sodium hydroxide (40 c.c.), and the cooled solution was shaken at room temperature and atmospheric pressure in the presence of palladised calcium carbonate (2·5 g.; 2% of palladium hydroxide). Absorption of hydrogen was complete after *ca.* 1½ hr.; then the mixture was filtered, the filtrate acidified (Congo-red) with hydrochloric acid (*d* 1·15), and the precipitate separated, washed with water, and dried. Crystallisation from acetone–light petroleum (b. p. 60—80°) gave 7-*hydroxy*-5-*methoxyphthalide* (830 mg., 77%) as prisms, m. p. 186—188° (Found: C, 60·1; H, 4·7. $C_9H_8O_4$ requires C, 60·0; H, 4·5%), $\lambda_{max.}$ 217 (ε 37,800), 255 (ε 15,600), and 291 mμ (ε 4300); $\nu_{max.}$ 1733 (in Nujol), 1748 cm.$^{-1}$ (in chloroform) (H-bonded phthalide C=O). This gave a purple colour with ferric chloride (cf. above).

(*b*) A solution of ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate (400 mg.) in dioxan (8 c.c.) was treated with water (2 c.c.), and the solution refluxed for 24 hr., concentrated under reduced pressure, allowed to cool, and filtered. Recrystallisation of the product from acetone–light petroleum (b. p. 60—80°) gave 7-hydroxy-5-methoxyphthalide (250 mg., 90%) as prisms, m. p. and mixed m. p. 185—187°, identical in infrared spectrum with preparation (*a*) in Nujol mull.

5,7-*Dimethoxyphthalide*.—5,7-Dihydroxyphthalide in methanol (10 c.c.) with ethereal diazomethane (*ca.* 1 hr.) gave 5,7-dimethoxyphthalide as needles (from chloroform–methanol), m. p. and mixed m. p. 151—153° (lit.,[4] m. p. 151—153°). The specimens had identical infrared spectra in Nujol [$\nu_{max.}$ 1748 (in Nujol), 1761 cm.$^{-1}$ (in chloroform) (phthalide C=O)].

5,7-Dimethoxyphthalide was also prepared by the action of diazomethane on 7-hydroxy-5-methoxyphthalide in 80% yield, and by hydrogenolysis (palladium–calcium carbonate) of 4,6-dibromo-5,7-dimethoxyphthalide in 75% yield or of 6-bromo-5,7-dimethoxyphthalide in 70% yield.

We thank the Department of Scientific and Industrial Research for an Award (to W. R. A.) and acknowledge the assistance, as indicated in the Experimental Part, given by Mr. James Highet, A.R.C.S.T.

THE ROYAL COLLEGE OF SCIENCE AND TECHNOLOGY,
GLASGOW.

[*Received, April 29th,* 1959.]

676. *The Structure of Floridean Starch. Part II.*[1] *Enzymic Hydrolysis and Other Studies.*

By Stanley Peat, J. R. Turvey, and J. M. Evans.

The Floridean starch of *Dilsea edulis* has been hydrolysed by β-amylase and α-amylase, in the absence and in the presence of R-enzyme. The products contain nigerose, from which it is concluded that the Floridean starch molecule contains a small proportion of α-1 : 3-links as an integral part of its structure. Evidence shows that Floridean starch is more closely related in structure to the plant amylopectins than to the animal glycogens. In particular, R-enzyme, which is without significant action on glycogens, causes debranching of Floridean starch to about the same extent as it does of waxy maize starch.

The average basal chain length of Floridean starch is found by periodate oxidation to be 15 glucose residues; comment is made on the variability of results determined by periodate oxidation methods.

The view that Floridean starch is a glucan of the amylopectin (or glycogen) type is supported by a study[1] of the di- and tri-saccharides liberated when the polysaccharide is partially hydrolysed by acid. It possesses a ramified structure in which the main chain-forming links are α-1 : 4-glucosidic, the branch links being α-1 : 6. The isolation of nigerose from the partial acid hydrolysate is a strong indication of the presence also of a small proportion of α-1 : 3-links. Account has to be taken, however, of the possibility that the nigerose had been produced by action of acid on the other sugars present and, although the nigerose was obtained in greater quantity than might be expected from reversion synthesis, further evidence was sought by a study of the hydrolysis of the starch by appropriate enzymes. It was expected that this investigation would shed light also on the question of the distribution of branch points in the Floridean starch structure, *i.e.*, the question as to whether this starch more nearly resembled glycogen or amylopectin in regard to degree of branching.

In preliminary experiments, Floridean starch (the same specimen as was used for acid hydrolysis, when digested with purified soya-bean β-amylase was converted into maltose to a limit of 42—43%. The sugar formed was shown by paper-chromatographic and by electrophoretic analysis to be primarily maltose. Nevertheless it contained a trace of a second disaccharide which had the R_F and M_G values of nigerose.

The same digest after inactivation of the β-amylase was subjected to the debranching action of R-enzyme (from broad bean[2]). It has been shown[3] that R-enzyme hydrolyses the branch links of amylopectin but those of glycogen are largely resistant to the enzyme. It became evident that at least a proportion of the branch linkages of Floridean starch were hydrolysed by the debranching enzyme when the successive actions of R-enzyme and β-amylase increased the β-amylolysis limit from 42 to 52% (see Table).

In a larger-scale experiment the starch was incubated with β-amylase until maximum conversion was attained (43%). From the digest the β-limit dextrin was isolated in good yield by removing the maltose by dialysis and precipitating the dextrin with ethanol. The β-limit dextrin ($[\alpha]_D$ +169°; B.V. 0·046) was now subjected to the successive actions of R-enzyme and β-amylase, and analysis of the digest at this second β-amylolysis limit showed that the dialysable sugar products included nigerose, the components of the mixture being identified as maltose, glucose, maltotriose, and nigerose, in diminishing order of yield.

The observation that only a trace of nigerose is liberated in the β-amylolysis of Floridean

[1] Part I, preceding paper.
[2] Hobson, Whelan, and Peat, *J.*, 1951, 1451.
[3] Peat, Whelan, Hobson, and Thomas, *J.*, 1954, 4440.

starch, suggests either that α-1 : 3-linkages do not occur in significant amounts in the starch or that the bulk of these linkages are to be found in the interior chains of the molecule. (An " interior chain " is defined as a chain, or part of a chain, between two adjacent branch points [4].) This question could be resolved by taking advantage of the facts that α-amylase, unlike β-amylase, fragments amylaceous polysaccharides by the scission of " inner " as well as " outer " α-1 : 4-linkages, and that the α-1 : 6-links in the fragments are more susceptible to the debranching action of R-enzyme than they are in the intact molecule. Accordingly, Floridean starch was digested successively with salivary α-amylase, R-enzyme, and again α-amylase. Dialysis of the final digest yielded a mixture of sugars in which, by chromatographic comparison with authentic specimens, panose, maltotriose, maltose, isomaltose, and nigerose were shown to be present. Separation of this mixture on thick filter paper gave a zone containing maltose and nigerose only. The presence of nigerose in this zone was confirmed by a comparison of R_F and M_G values with those of the authentic disaccharide. The conclusion is unavoidable that the nigerose isolated is not an artifact but that the α-1 : 3-glucosidic link is an integral, though minor, part of the structure of Floridean starch.

Comparison of Floridean starch, amylopectin (waxy maize) and animal glycogen.

	Common animal glycogens	Floridean starch	Waxy maize starch
Blue value [a]	0·02	0·065	0·16
* $\lambda_{max.}$ (mμ)	420—490 [b]	530	520 [e]
β-Amylolysis limit (% maltose)	40—50 [c]	42	52 [f]
Increase in β-amylolysis limit by R-enzyme (%)	0	10	12 [f]
Basal chain length (glucose units)	10—14 [d]	15	20 [g]

* Wavelength of peak absorption of iodine complex.

[a] Bourne, Haworth, Macey, and Peat, *J.*, 1948, 924. [b] Manners, *Adv. Carbohydrate Chem.*, 1957, **12**, 278. [c] Liddle and Manners, *J.*, 1957, 3432. [d] Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **78**, 994. [e] Barker, Bourne, and Peat, *J.*, 1949, 1712. [f] Peat, Whelan, and Thomas, *J.*, 1956, 3026. [g] Anderson, Greenwood, and Hirst, *J.*, 1955, 225.

In the Table, Floridean starch is compared with an average glycogen on the one hand and waxy maize starch (*i.e.*, amylopectin) on the other. Too much importance can be attached to comparisons of this kind but the evidence favours the view that Floridean starch is better described as an amylopectin than as a glycogen. In particular, we draw attention to the effect of R-enzyme and to the comparison of basal chain lengths.

If susceptibility to the debranching action of R-enzyme is accepted as a criterion,[3] then Floridean starch is an amylopectin and not a glycogen. Fleming and Manners however, describe [5] an 18-unit glycogen (from rabbit liver) which is attacked by R-enzyme (β-amylolysis limit raised from 51 to 58%) and these authors express the view that " the specificity of R-enzyme is controlled not by the degree of branching in the substrate, or the exterior chain length, but by the average length of the interior chains." This minimum interior chain length is calculated to be 5 glucose units. If this view is accepted then it would follow that the average number of glucose units between branch points in the Floridean starch molecule is greater than 5 (see below). It should be mentioned that the debranching enzyme of yeast, isoamylase,[6] also raises the β-amylolysis limit of Floridean starch but this enzyme is less specific than R-enzyme inasmuch as it also has a debranching action on normal animal glycogens.

The comparative values given in the Table for basal chain length need some comment. " Basal (or 'repeating') chain length " is a convenient term for expressing the number of monosaccharide units per non-reducing end unit in a polysaccharide molecule. Since in a large branched molecule, the number of non-reducing ends is the same as the number

[4] Manners, *Ann. Reports*, 1953, **50**, 289.
[5] Fleming and Manners, *Chem. and Ind.*, 1958, 831.
[6] Maruo and Kobayashi, *Nature*, 1951, **167**, 606; Manners and Khin Maung, *Chem. and Ind.*, 1955, 950.

of branch points, it follows that the basal chain length is a measure of the degree of branching. The value of 15 was determined by periodate oxidation of the Floridean starch under the conditions described by Peat, Whelan, and Turvey [7] and estimation of the formic acid produced. The periodate method continues to present difficulties of interpretation because the course of oxidation is strongly influenced by the experimental conditions employed. For example, the basal chain length of Floridean starch was found by Barry, Halsall, Hirst, and Jones [8] to be 18 and by O'Colla [9] to be 12. More recently, Fleming, Hirst, and Manners,[10] who find a value of 9 for the basal chain length of Floridean starch, attributed the variability of earlier results to the varying degree of completeness of oxidation achieved by different experimental methods. The position is further complicated by the ease with which over-oxidation can occur (with the consequent liberation of additional formic acid) in certain circumstances.[11] It was thus clearly desirable that comparisons should be made, when possible, under identical experimental conditions. For this reason the glycogen of fœtal sheep liver, kindly supplied by Dr. D. J. Bell, was oxidised by sodium metaperiodate by exactly the same procedure as we used in the oxidation of the Floridean starch. The basal chain length was thus estimated as 12, in close agreement with the value (13) previously reported by Bell and Manners [12] for the same specimen of glycogen. The figures (10—14) given in the Table for the basal chain lengths of animal glycogens are those of Abdel-Ahker and Smith,[13] who examined, by periodate oxidation, 37 specimens of glycogen from different sources. The limits of deviation from the average value of 12 glucose units were 10 and 14.

The value we find by periodate oxidation for the average basal chain length of Floridean starch is supported by the argument that if for R-enzyme action the minimum number of glucose residues separating adjacent branch points averages 5 (Fleming and Manners [5]), and the observed β-amylolysis limit is 42—43% then it follows that the average basal chain length of our specimen of Floridean starch is at least 15.

It is concluded that if α-1 : 3-linkages are not an integral part of the structure of Floridean starch then the isolation of nigerose means that this disaccharide is synthesized from some other sugar, not only by preparations of β-amylase but also of α-amylase and R-enzyme, a highly unlikely proposition, and secondly, that in respect of degree of branching, Floridean starch is more closely related to plant amylopectins than to animal glycogens.

Experimental

General Methods.—The methods of paper chromatography and electrophoresis were as described.[1] The determination of reducing power and of blue value, and the oxidation of polysaccharides with periodate followed the methods described by Peat *et al.*[7] Purified soya-bean β-amylase was prepared by the method of Peat *et al.*[14] and contained no detectable Z-enzyme or α-amylase. R-Enzyme, prepared from broad beans by the method of Hobson *et al.*,[3] was free from detectable amylase impurity. During enzymic hydrolysis, all digests were covered with toluene to prevent contamination with micro-organisms. The concentration of polysaccharide in a solution was determined by Pirt and Whelan's method.[15] The Floridean starch sample was that described previously.[1]

Light-absorption Curves.—The starch (3 mg.) was dissolved in warm water and cooled, and 3N-hydrochloric acid (0·5 ml.) was added. Iodine solution (2 ml., containing 2 mg. of iodine and 20 mg. of potassium iodide per ml.) was added and the solution diluted to 100 ml. The light absorption was measured in a Unicam S.P. 500 spectrophotometer in 1 cm. cells at various

[7] Peat, Whelan, and Turvey, *J.*, 1956, 2317.
[8] Barry, Halsall, Hirst, and Jones, *J.*, 1949, 1468.
[9] O'Colla, *Proc. Roy. Irish Acad.*, 1953, **55**, *B*, 321.
[10] Fleming, Hirst, and Manners, *J.*, 1956, 2831.
[11] Whelan, "Encyclopedia of Plant Physiology," Springer-Verlag, Berlin, 1956, Vol. VI, p. 164.
[12] Bell and Manners, *J.*, 1952, 3641.
[13] Abdel-Ahker and Smith, *J. Amer. Chem. Soc.*, 1951, **78**, 994.
[14] Peat, Pirt, and Whelan, *J.*, 1952, 714.
[15] Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224.

wavelengths, and the wavelength of peak absorption found by interpolation (533 mμ). Increasing the amount of iodine solution from 2 to 8 ml. did not affect the position of the peak. Two other samples of Floridean starch were also examined, one isolated by Lawley [16] and the other a gift from Professor E. L. Hirst. Both samples showed $\lambda_{max.}$ 527 mμ.

The Action of β-Amylase and R-Enzyme.—The initial digest contained Floridean starch (82 mg.), 0·2M-acetate buffer (pH 4·8; 5 ml.), and β-amylase (800 units) in 50 ml. A digest containing the reagents but without starch was used throughout as a blank. The digests were incubated at 35°, and portions (2 ml. each) examined at intervals. Between 2 and 44 hr. the reducing power remained practically constant, corresponding to a conversion into maltose of 42·1%. After 44 hr. a portion (20 ml.) of each digest was heated at 100° for 3 min. to inactivate the β-amylase, and cooled; the pH was then adjusted to 7·0 with 1N-sodium hydroxide. R-Enzyme (50 mg.; 1 ml.) was added to each digest and the volumes were adjusted to 25 ml. After incubation at 35° for 6 hr., the digests were heated at 100° for 10 min. and cooled. A portion (4 ml.) was removed from each digest for estimation of reducing power (after deproteinisation) and these indicated a conversion (as maltose) of 43·1%. The pH of a second portion (20 ml.) was adjusted to 4·8 with 1N-acetic acid, β-amylase (800 units) was added, and the digests were diluted to 25 ml. Further incubation at 35° and estimation of reducing power indicated that the conversion (as maltose) remained constant after 21 hr. at 53·8%.

Large-scale β-Amylolysis.—Floridean starch (1·26 g., corr. as $C_6H_{10}O_5$) was incubated at 35° with β-amylase (8000 units) and 0·2M-acetate buffer (pH 4·8; 30 ml.) in a total volume of 500 ml. Portions (2 ml. each) were examined at intervals for reducing power. After 6 hr. the reducing power remained constant at a conversion into maltose of 43·3%. After 24 hr. the digest was heated at 100° for 5 min., cooled, and dialysed against water (4 × 400 ml.) during 36 hr. The dialysate was concentrated to dryness at pH 6—7, the sugars extracted with 80% methanol, the extracts evaporated to dryness, and the residues examined by paper chromatography and electrophoresis (see discussion). The impermeate was concentrated to 300 ml., the concentrate poured into ethanol (1 l.), and the precipitated β-limit dextrin collected (centrifuge) washed, and dried (yield 0·64 g.). The blue value and specific optical rotation (*c* 0·16 in water) were determined. The β-limit dextrin (*ca.* 40 mg.) was incubated at 35° with R-enzyme (100 mg.; 2 ml.) and 0·2M-acetate buffer (pH 7·0; 3 ml.) in a total volume of 50 ml. After 6 hr. the digest was heated at 100° for 5 min. and then cooled, and the pH adjusted (acetic acid) to 4·8. The digest was incubated at 35° for a further 40 hr. with β-amylase (800 units). The digest was dialysed against water (4 × 100 ml.) and the sugars were isolated from the dialysate and examined as before.

Action of α-Amylase and R-Enzyme.—The α-amylase was prepared by diluting saliva with an equal volume of water and centrifuging to remove precipitated mucins. Floridean starch (200 mg.) was incubated at 35° with α-amylase (2 ml.) and 0·2M-acetate buffer (pH 7·0; 6 ml.) in a total volume of 100 ml. After 30 min. the digest was heated at 100° for 5 min., cooled, and incubated at 35° with R-enzyme (300 mg.) for 6 hr. The digest was again heated at 100° for 5 min. and then cooled, and α-amylase (5 ml.) added. After 1 hr. at 35° the digest was dialysed against water (2 × 600 ml.), and the sugars were isolated from the dialysate as before. Paper chromatography indicated the presence of maltotriose, panose, isomaltose, maltose, nigerose, and glucose. The mixture was fractionated by thick-paper chromatography in the butan-1-ol–pyridine–water solvent system in which isomaltose can be separated from maltose and nigerose.[1] The zone containing maltose and nigerose was cut out and eluted with water, and the constituent sugars examined by paper chromatography in the butan-1-ol–acetic acid–water solvent system and by electrophoresis in borate buffer.[1] In both cases a zone migrating with the same mobility as nigerose was detected in addition to the maltose zone.

We thank the Department of Scientific and Industrial Research for a grant to one of us (J. M. E.).

UNIVERSITY COLLEGE OF NORTH WALES, BANGOR. [*Received, May 4th*, 1959.]

[16] Lawley, Ph.D. Thesis, Wales, 1955.

677. *The Interpretation of the Energies of Activation of some Reactions of Aromatic Nitro-compounds.*

By E. F. Caldin

The factors influencing the energy of activation of bimolecular reactions in solution are reviewed, with special attention to the energy required for the reorganisation of solvent molecules. The conclusions are applied to the interpretation of the energies of activation of the reactions of ethoxide ion with various aromatic nitro-compounds; these reactions include proton-transfer, complex-formation, and addition-compound formation. It is concluded that the energy required to reorganise solvent molecules is considerable, and may account for the greater part of the observed activation energy, not only for complex-formation but for proton-transfer.

In earlier papers the kinetics and mechanisms of the various reactions of ethoxide ion with a series of related aromatic trinitro-compounds have been considered.[1-4] These nitro-compounds are 2,4,6-trinitrotoluene (T.N.T.), 2,4,6-trinitroanisole (T.N.A.), and 1,3,5-trinitrobenzene (T.N.B.). The solvent was ethanol plus 1% of toluene by weight. The reactions, and the values found for the Arrhenius and other parameters, are summarised in Table 1. Most of the reactions are reversible; E_1 and A_1 denote the energy of activation and A-factor for the forward reaction, while E_{-1} and A_{-1} refer to the reverse reaction.

Table 1.

Reaction of ethoxide ion with	Mechanism	E_1 (kcal. mole^{-1})	$\log_{10} A_1$ (l. mole sec.$^{-1}$)	E_{-1} (kcal. mole^{-1})	$\log_{10} A_{-1}$ (sec.$^{-1}$)	ΔH (kcal. mole^{-1})	$\Delta S°$ (cal. deg.$^{-1}$ mole^{-1})
(*a*) T.N.T., " slow "	Proton-transfer	13·6	12·0	10·$_0$	6·1	3·6	27
(*b*) T.N.A., " fast "	Complex-formation	10·4	10·7	13·7	12·3	−3·3	−8
(*c*) T.N.B.	Complex-formation?	11·7	13·3	11·4	9·9	0·3	16
(*d*) T.N.T., " fast "	Complex-formation?	12·4	12·3	8·$_3$	7·$_4$	4	22
(*e*) T.N.A., " slow "	Addition-compound formation	13·1	10·9	—	—	—	—

The mechanisms assigned in Table 1 are established most firmly for reactions (*a*), (*b*), and (*e*). In favour of the proton-transfer mechanism for reaction (*a*) is the evidence of the Brønsted relation for the reverse reaction with various acids.[1] In favour of the addition-compound mechanism for reaction (*e*) is the evidence that identical products are obtained from the reactions of ethoxide ion with trinitroanisole and that of methoxide ion with trinitrophenetole.[2] The view that the product of reaction (*b*) is some kind of complex (whether a charge-transfer complex or an ion-dipole complex) is the most obvious interpretation of the fact that the reaction occurs in the same mixture as reaction (*e*) but very much faster.[2] Reactions (*b*) and (*c*) are regarded as complex-formations[3,4] though the evidence does not exclude the formation of addition compounds as in reaction (*e*).[5]

All the values of $\log_{10} A_1$ lie in the range 10·7 to 13·3 when A_1 is in l.·mole^{-1} sec.$^{-1}$. That some of these values are greater than the usual value of about 11·5 for ion-dipole reactions can be understood in general terms, since the charge which is originally mainly on the oxygen of the ethoxide ion will become distributed in the transition state, so that partial desolvation will occur and lead to a positive contribution to the entropy of activation.

[1] Caldin and Long, *Proc. Roy. Soc.*, 1955, *A*, **228**, 263.
[2] Ainscough and Caldin, *J.*, 1956, 2528.
[3] Ainscough and Caldin, *J.*, 1956, 2540.
[4] Ainscough and Caldin, *J.*, 1956, 2546.
[5] Foster, *Nature*, 1959, **183**, 1042.

The considerable positive values of ΔS^0 for several of the reactions are in accord with this explanation.

The values found for the Arrhenius energy of activation E_1 all lie in the range 10·4 to 13·6 kcal. mole^{-1}. Since they refer to reactions of three different mechanisms, involving closely similar molecules, they give rise to some interesting comparisons. These must be prefaced by some general considerations about energies of activation.

Energies of Activation of Bimolecular Reactions in Solution.—Four different factors can contribute to the energy of activation E of a bimolecular reaction in solution: (i) The stretching of bonds in the reacting molecules, and the incipient formation of new bonds. (ii) Repulsion between unbonded atoms on close approach. (iii) Electrostatic interactions between the reactant molecules (ion-ion, ion-dipole, or dipole-dipole). (iv) Reorganisation of solvent molecules, first to allow the reactant molecules to come together, and then to form the solvated transition state. These factors have long been recognised;[6,7] their relative contributions, however, are still unknown for most reactions, and will probably depend markedly on the reaction. The present results call attention to factor (iv). Evidence on the contributions of these four factors may be briefly recalled.

(i) *Energies of bonds broken and formed in the reactant molecules.* That the breaking and making of covalent bonds in the reactant molecules is the main factor influencing E in many reactions has been commonly assumed on the basis of general chemical experience, supported by the moderate success of the London–Eyring–Polanyi method of calculating E for simple gas reactions. Experimental support is forthcoming from results on gas reactions of two classes: unimolecular reactions, for which E shows approximate agreement with independently-determined values of the dissociation energy D of the relevant bond; and radical reactions, which show a correlation between E and ΔH, so that Semenov has made extensive use of the assumption that E is to a first approximation a function of the difference between the energies of the bonds broken and formed.[8] For gas reactions between molecules, however, there are no satisfactory correlations with D or ΔH. Various authors have pointed out apparent parallelisms between E and D for relevant bonds,[9-12] but these relations are neither precise nor certain.[13] That a simple general relation between E and the various D's is not to be expected is shown by an investigation of the reactions between sodium and aryl halides, where the absence of such a relation is attributable to stabilisation of the transition state by resonance.[14] For reactions in solution, relations between E and D have not been reported. The Brønsted equation for acid–base catalysis can be derived from a potential-energy picture in which the activation energy is applied entirely to the stretching of a bond, but not all the consequences of this picture agree with experiment.[15] Nevertheless, the energy required to stretch bonds is clearly often an important contribution to E.

(ii) *Short-range repulsion.* The contribution to E arising from interpenetration of electron shells as atoms approach closely is not in general easy to estimate. It rises steeply as the distance r decreases, and has been expressed either as an exponential or as a term in r^{-12}. Some detailed calculations suggest that the contribution is important;[6,16] others, however, suggest that to a first approximation it can be omitted.[17] For proton transfer, $AH + B \longrightarrow A^- + BH^+$, the atom transferred has no valency electrons and so

[6] Ogg and Polanyi, *Trans. Faraday Soc.*, 1935, **31**, 604.
[7] Evans and Polanyi, *Trans. Faraday Soc.*, 1938, **34**, 11.
[8] Semenov, "Some Problems of Chemical Reactivity and Kinetics," Vol. I, Pergamon Press, London, 1958.
[9] Hirschfelder, *J. Chem. Phys.*, 1941, **9**, 645.
[10] Evans and Warhurst, *Trans. Faraday Soc.*, 1939, **35**, 593.
[11] Trotman-Dickenson, *Discuss. Faraday Soc.*, 1951, **10**, 111.
[12] Frost and Pearson, "Kinetics and Mechanism," Chapman & Hall, London, 1953, pp. 101, 102.
[13] Trotman-Dickenson, "Gas Kinetics," Butterworths, London, 1955, p. 230.
[14] Riding, Scannell, and Warhurst, *Trans. Faraday Soc.*, 1956, **52**, 1364.
[15] Bell, "Acid-base Catalysis," Oxford, 1941, Ch. 8.
[16] Evans and Warhurst, *Trans. Faraday Soc.*, 1939, **35**, 593.
[17] Baughan and Polanyi, *Trans. Faraday Soc.*, 1941, **37**, 648.

is not subject to these short-range repulsive forces. Repulsion between the atoms A and B may still be appreciable, but Bell's calculations [18] make it unlikely that the contribution to E from repulsion will be greater than about 15% of the whole in a proton-transfer reaction.

(iii) *Electrostatic interactions.* The relatively long-range interactions between reactant ions or dipoles appear to have an important effect on E in certain reactions in solution. The most direct evidence is that in various series of related reactions the variations in E can be correlated with those of the dipole moments of the reactants, or with the known order of the inductive effects of substituents.[19,20]

(iv) *Reorganisation of solvent molecules.* In reactions in solution, there will generally be some reorganisation of the solvating molecules round the reactants. Two aspects of these solvation changes can be distinguished. (*a*) Solvated molecules cannot approach close enough to react unless at least one solvating molecule is detached from each; and if a molecule is charged, the energy required to remove a polar solvent molecule is considerable. (*b*) On forming the transition state there may be changes in the orientation of molecules in the solvation shell and in the restrictions on their motions. The evidence that these solvation changes affect E is as follows.

(*a*) Taube's experiments on the rate of exchange of $H_2{}^{18}O$ with solutions of aluminium salts [21] have shown that the activation energy for the substitution reaction of $Al(H_2O)_6$ with $H_2{}^{18}O$ is of the order of 20 kcal. mole^{-1}. Thus, considerable energy is concerned in removing a water molecule from the ion. Calculations of solvation energies had previously pointed to this conclusion. For hydroxide ion in water, on the assumption that each OH^- is co-ordinated to six water molecules, and that its heat of hydration is equal to that of the fluorine ion which is known from thermal data, the energy required to remove one solvent molecule has been calculated as 20·7 kcal. mole^{-1}, equal to nearly the whole of the observed value of E for the hydrolysis of methyl halides by the hydroxyl ion in water. This led Moelwyn-Hughes and Glew [22] to consider the hypothesis that most of E represents work done in reorganisation of the solvent molecules which solvate the ion. That this energy is an important contribution to E is suggested also by the considerable magnitudes of the heats of solvation of halide ions [23] and of carbonium ions [24] in water and alcohols; these have been used by Franklin [24] in calculations of E for the solvolysis of alkyl halides, and the calculated values are within a few kcal. mole^{-1} of those determined experimentally. It seems, therefore, that, in some reactions at least, the process of desolvation before reaction can require considerable activation energy. Some further evidence suggesting a distinction between this preliminary desolvation and the overall change of solvation on forming the transition state is provided by the effect of pressure on the exchange reaction of $H_2{}^{18}O$ with the pentammino-aquo cobaltic ion.[25]

(*b*) The evidence for changes of solvation when the transition state is formed is well known. The A-factors of reactions in solution, especially those involving changes in magnitude or distribution of charge, can often be explained in these terms.[26] The changes in A when the pressure is increased,[27,28] and when the solvent is changed,[29,30] can often be interpreted in the same way. These solvation changes should contribute to E, as has been suggested by Libby [31] for electron-exchange reactions.

[18] Bell, *Trans. Faraday Soc.*, 1944, **37**, 493.
[19] Hinshelwood, Laidler, and Timm, *J.*, 1938, 848.
[20] Moelwyn-Hughes, "Kinetics of Reactions in Solution," Oxford, 1947, Ch. 4, 5, 7.
[21] Hunt and Taube, *J. Chem. Phys.*, 1951, **19**, 602; Baldwin and Taube, to be published.
[22] Moelwyn-Hughes and Glew, *Proc. Roy. Soc.*, 1952, *A*, **212**, 260.
[23] Latimer, Pitzer, and Slansky, *J. Chem. Phys.*, 1939, **7**, 108.
[24] Franklin, *Trans. Faraday Soc.*, 1952, **48**, 443.
[25] Hunt and Taube, *J. Amer. Chem. Soc.*, 1958, **80**, 2642.
[26] Bell, *J.*, 1943, 629.
[27] Hamann, "Physico-chemical Effects of Pressure," Butterworths, London, 1957, Ch. 9.
[28] Burrell and Laidler, *Trans. Faraday Soc.*, 1955, **51**, 1497.
[29] Pearson, *J. Chem. Phys.*, 1952, **20**, 1478.
[30] Caldin and Peacock, *Trans. Faraday Soc.*, 1955, **51**, 1217.
[31] Libby, *J. Phys. Chem.*, 1952, **56**, 863.

The most direct evidence comes from solvent effects. The effect of change of solvent on E is often considerable; for several reactions the variations are greater than 5 kcal. mole^{-1}.[30,35-42] These observed changes in E will reflect changes in the energy required for the reorientation of solvent molecules when the transition state is formed. Two factors seem to be concerned in the variations of E with solvent. First, a change of solvent will be expected to alter the electrostatic interactions considered in (iii), since they depend on the dielectric constant. Calculations from simple models indicate that E will be appreciably affected,[29,30,32] and that in a polar solvent of dielectric constant even as low as 5 the electrostatic contribution to E will be about double that in a non-polar solvent.[29] The experimental results do not always agree with these predictions, however, especially when the range of solvents is wide. A survey of reactions which involve a large change in polarity, such as Menschutkin reactions, led to the conclusion that, except perhaps for aliphatic solvents, the electrostatic picture is inadequate.[30] It has been pointed out [29] that the electrostatic contribution to E should be nearly the same for all solvents with even a moderate dielectric constant, so that the differences often found for water, ethanol, and acetone [30,36-39,42] are anomalous from the electrostatic point of view. Anomalies in infrared spectra [33] and equilibria [34] have also been reported. More specific interactions must therefore be considered as well. These may be solvent–solute or solvent–solvent interactions. As regards the first of these, we must expect a considerable contribution to E if solvent molecules are attached to one or both of the reactants, but not to the transition state, by hydrogen bonding or any other specific attraction which has to be overcome before the reactants can approach each other in the correct orientation. Specific solvation of this kind has been invoked to explain results on the nitramide reaction catalysed by dimethylaniline.[30] As regards the second type, we should expect that in hydroxylic solvents hydrogen bonding would affect E, since the rearrangement of solvent molecules will involve the breaking of solvent–solvent bonds. This may account for the much higher values for E often found in hydroxylic solvents compared with benzene or even with non-hydroxylic aliphatic solvents.[30]

These four terms contributing to E will be assumed as a first approximation to be independent and additive. Thus we write,

$$E = E\text{ (bonding)} + E\text{ (repulsion)} + E\text{ (electrostatic)} + E\text{ (solvation)} \quad . \quad (1)$$

Application to the Present Results.—Consider first the proton-transfer reaction between T.N.T. and ethoxide [reaction (*a*) of Table 1], which we can write as $ArCH_3 + OEt^- \longrightarrow ArCH_2^- + EtOH$. The observed energy of activation (13·6 kcal. mole^{-1}) will be shared among the four factors distinguished above. However, since the reaction is a proton-transfer, E (repulsion), will be small, probably not more than about 2 kcal. mole^{-1}. A value for the electrostatic contribution can be calculated on the assumptions that the negative charge of the ethoxide ion is concentrated on the oxygen atom, and that it interacts mainly with the C–H dipole. This will be an induced dipole modified by the permanent dipole; we can treat the corresponding energies as additive. The permanent dipole, if it can be assumed to be similar to that in methane, has a magnitude of about 0·4 D, probably with the hydrogen as negative end,[43] so that the ion will be repelled.

[32] Moelwyn-Hughes, " Kinetics of Reactions in Solution," Oxford, 1947, Ch. 7.
[33] Bellamy *et al.*, *Trans. Faraday Soc.*, 1959, **54**, 14, 220.
[34] Ross and Labes, *J. Amer. Chem. Soc.*, 1955, **77**, 4916.
[35] Cox, *J.*, 1921, 142.
[36] Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 5937.
[37] Hinshelwood *et al.*, *J.*, 1936, 1353; 1937, 538, 1573.
[38] Brown and Hudson, *J.*, 1950, 3259.
[39] Brown and Hudson, *J.*, 1953, 3352.
[40] Syrka and Gladischev, *Acta Physicochim. U.R.S.S.*, 1935, **2**, 291.
[41] Alder and Leffler, *J. Amer. Chem. Soc.*, 1954, **76**, 1425.
[42] Sweet and Le Roux, *J.*, 1956, 2110.
[43] Smith, " Electric Dipole Moments," Butterworths, London, 1955, Ch. 5.

The energy associated with this repulsion is $e\mu/\varepsilon r^2$, where e is the electronic charge, μ the dipole moment, and ε the dielectric constant. When r is taken as about 2·8 Å (from Bell's calculations [18]), the energy becomes $3{\cdot}3/\varepsilon$ kcal. mole^{-1}. The induced dipole will be attracted by the ion; the energy is $\frac{1}{2}\alpha e^2/\varepsilon a^4$, where α is the polarisability of the C–H bond and may be taken [44] as $7{\cdot}9 \times 10^{-25}$ cm.^{3}, and a is the distance from the centre of the ion to the middle of the C–H bond. This gives $13/\varepsilon$ kcal. mole^{-1}. Thus the overall electrostatic effect is an attraction associated with an energy of about $10/\varepsilon$ kcal. mole^{-1}. The calculation has ignored the effect of the neighbouring dipoles, but is probably correct as regards order of magnitude. The contribution E(electrostatic) can therefore be taken as about $-10/\varepsilon$ kcal. mole^{-1}. It is not easy to decide what value to adopt for the dielectric constant ε. The bulk value is clearly inapplicable; a valve between 3 and 1 is probably correct.

The dielectric constant first being taken as 3, E(electrostatic) becomes about -3 kcal. mole^{-1}; with E(repulsion) $\simeq$ 2 kcal. mole^{-1}, this gives E(electrostatic) + E–(repulsion) $\simeq$ -1 kcal. mole^{-1}. Since the experimental value of E is 13·6 kcal. mole^{-1}, eqn. 1 gives for the proton-transfer (*a*):

$$E(\text{bonding}) + E(\text{solvation}) \simeq 15 \text{ kcal. mole}^{-1}, \text{ if } \varepsilon = 3 \quad . \quad . \quad . \quad (2)$$

Consider next the complex-formation between T.N.A. and ethoxide ion [reaction (*b*) of Table 1], which we can write: T.N.A. + OEt^- ⟶ (T.N.A.,$OEt)^-$. Here no bond is broken, and the activation energy for the formation of the " bond " in the complex will be low, whether it is due to charge-transfer [45] or to ion-dipole interaction; thus E(bonding) $\simeq$ 0. It is difficult to estimate E(repulsion) and E(electrostatic), since the relative positions of the ethoxide ion and the T.N.A. molecule are not known, but it seems reasonable to assume that for this relatively loose complex-formation their joint contribution to E will be even less than for the proton-transfer (*a*). In that case, the major contribution to E will be from factor (iv), the reorientation of solvent molecules. Thus for reaction (*b*) and with the observed value of E (10·4 kcal. mole^{-1})

$$E(\text{solvation}) \simeq 10 \text{ kcal. mole}^{-1}, \text{ if } \varepsilon = 3 \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Reactions (*c*) and (*d*) will have, on the same assumptions, similar values for E(solvation), namely about 11 and 12 kcal. mole^{-1}. Thus it appears that the contribution to E for these reactions from the solvent reorganisation is in the region of 10 kcal. mole^{-1}—a considerable amount—and this for an ion-dipole reaction involving no change of charge.

This conclusion is confirmed if we take account also of the results for the reverse reactions, *i.e.* the unimolecular dissociations of the complexes formed in reactions (*b*), (*c*), and (*d*). Consider first reaction (*b*). For the reverse dissociation, the terms E(repulsion) and E(electrostatic) will be equal to those for the complex-formation but of opposite sign, while E(bonding) will again be small. The sum of the energies of activation for the forward and back reactions will therefore, by eqn. 1, be nearly equal to the sum of the two E(solvation) terms, and their mean will give the mean value of E(solvation) for the forward and reverse reactions. From the values given in Table 1, the mean E(solvation) comes to 12 kcal. mole^{-1} for reaction (*b*). The corresponding value for reaction (*c*) is 12, and that for reaction (*d*) is 10 kcal. mole^{-1}. The separate values for the forward and reverse reactions cannot be found from this argument, but it would seem that the order of magnitude given in eqn. 3 is correct.

We may next compare the results for the proton-transfer and complex-formation reactions of T.N.T. [reactions (*a*) and (*d*)]. We might expect E(solvation) to be about the same for the two reactions, and this expectation is confirmed by the fact that the A-factors are equal within experimental error (Table 1). Then, if the value given above for reaction (*d*) is used, E(solvation) for reaction (*a*) will be not far from 12 kcal. mole^{-1}. Eqn. 2 then

[44] Denbigh, *Trans. Faraday Soc.*, 1940, **36**, 936.
[45] Mulliken, personal communication, and *J. Phys. Chem.*, 1952, **56**, 801.

implies that E(bonding) is small for the proton-transfer (*a*)—not more than a few kcal.—and that E(solvation) is the main contribution to E for this reaction.

It is difficult to draw detailed conclusions about the addition reaction (*e*), for which $E = 13{\cdot}1$ kcal. mole^{-1}. If the desolvation energy is about the same as for the other reactions, it accounts for most of E, so that E(bonding) + E(repulsion) + E(electrostatic) $\simeq 0$. If E(electrostatic) can be assumed to be small compared with the other terms, this gives E(repulsion) $\simeq -E$(bonding). But it would be difficult to assign a numerical value to either of these terms.

If we take the dielectric constant as 1 instead of 3, the numerical values are different but we still reach the conclusions that E(solvation) is considerable and that it forms at least a considerable fraction of E for the proton-transfer. For this reaction, E(electrostatic) becomes about -10 kcal. mole^{-1}, whence E(electrostatic) + E(repulsion) $\simeq -8$ kcal. mole^{-1}, and eqn. 2 becomes:

$$E(\text{bonding}) + E(\text{solvation}) \simeq 23 \text{ kcal. mole}^{-1}, \text{ if } \varepsilon = 1 \quad . \quad . \quad . \quad (2')$$

For the complex-formation, if we suppose that E(electrostatic) + E(repulsion) lies between 0 and the above value of -8 kcal. mole^{-1}, eqn. 3 becomes:

$$E(\text{solvation}) \simeq 10 \text{ to } 18 \text{ kcal. mole}^{-1}, \text{ if } \varepsilon = 1 \quad . \quad . \quad . \quad . \quad (3')$$

Comparing eqn. 2′ and 3′, we see that if E(solvation) has similar values for the two reactions, it is a considerable contribution to the total energy of activation for the proton-transfer.

The main conclusions are that in this set of reactions in ethanol: (*a*) The contribution to E of the energy required to reorganise solvent molecules appears to be considerable, of the order of 10 kcal. mole^{-1} or more, and (*b*) that it accounts for the greater part of E, not only in complex-formation but in proton-transfer.

I thank Dr. R. S. Bradley for helpful discussions.

PHYSICAL CHEMISTRY DEPARTMENT, THE UNIVERSITY, LEEDS, 2. [*Received, May 12th,* 1959.]

---

678. *Tocopherols. Part III.* Reaction of Phytol with Some Toluquinol Derivatives.*

By P. MAMALIS, J. GREEN, S. MARCINKIEWICZ, and D. MCHALE.

The preparation of some toluquinol derivatives is described and their reaction with phytol investigated.

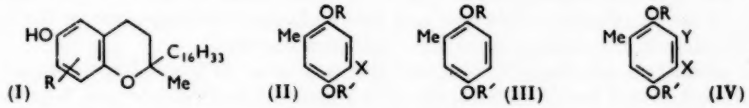
WHEREAS 2,3,5-trimethylquinol and the three dimethylquinols condense with phytol to give in each case only one tocol, toluquinol can theoretically give rise to three tocols, 5-, 7-, and 8-methyltocol (I; R = Me). Reaction of toluquinol with phytol was first carried out by Karrer and Fritzsche [1] who obtained a mixture of monomethyltocols of undetermined composition. Recently, Pendse and Karrer [2] identified 7-methyltocol and stated that smaller quantities of isomeric monomethyltocols may also have been present in the reaction product. Work in these laboratories [3] showed that under the conditions of the Swiss workers, all three tocols are formed, the ratios of 5- : 7- : 8-methyltocol being 1 : 2 : 1, respectively.

In connection with the synthesis of 5-methyltocol, we investigated the reaction of phytol with suitably substituted toluquinols (II; R′ = H) that might be expected to lead to isomer-free 5-methyltocol derivatives. Some toluquinol derivatives have therefore been

* Part II, *J.*, 1958, 1850.

[1] Karrer and Fritzsche, *Helv. Chim. Acta*, 1939, **22**, 260.
[2] Pendse and Karrer, *ibid.*, 1958, **41**, 396.
[3] Marcinkiewicz, McHale, Mamalis, and Green, *J.*, 1959, 3377.

prepared and their reaction with phytol studied. Benzoylation of toluquinol in pyridine has been stated to yield a mixture of the dibenzoate and 4-benzoate (III; R = R′ = Bz, and R = H, R′ = Bz respectively).[4] A sample of toluquinol 4-benzoate prepared in this way gave, on treatment with benzyl bromide in acetone, a mixture of two substances, (A) m. p. 118—119°, and (B) m. p. 87—89°. Both products gave correct analyses for benzoyloxybenzyloxytoluene and appeared to be isomers; clearly our sample of toluquinol



4-benzoate, although having an m. p. in accordance with the literature, must have been contaminated with some of the 1-benzoate (III; R = Bz, R′ = H). Hydrogenation of substance (A) afforded a toluquinol benzoate, m. p. 120—122°, assumed to be pure 4-benzoate (Jacob, Sutcliffe, and Todd [4] gave m. p. 113° for this compound, its structure being assigned by analogy with the monoalkylation product of toluquinol), while hydrogenation of substance (B) yielded toluquinol 1-benzoate, m. p. 145—146°. It follows that substance (A) was 5-benzoyloxy-2-benzyloxytoluene (III; R = CH_2Ph, R′ = Bz), and substance (B) its isomer. Alkaline hydrolysis of (A) furnished toluquinol 1-benzyl ether (III; R = CH_2Ph, R′ = H); similarly (B) afforded the 4-benzyl ether. The tedious separation of the monobenzoates was later found unnecessary, benzylation of the crude product giving a readily separable mixture of (A) and (B). Benzylation of toluquinol afforded toluquinol dibenzyl ether and a mixture of toluquinol monobenzyl ethers: the latter on benzoylation yielded substance (B) as the sole crystalline product.

Bromination of toluquinol 1-benzyl ether in chloroform yielded 5-bromotoluquinol 1-benzyl ether (II; R = CH_2Ph, R′ = H, X = Br) together with some 5-bromotoluquinol.[5] Addition of calcium carbonate to the bromination mixture prevented the rather easy cleavage of the bromobenzyl ether, the structure of which was confirmed by its hydrogenation to 5-bromotoluquinol. When the ether was heated with phytol in benzene–formic acid, a dark oil was obtained. Paper-chromatographic examination [6] of the oily product obtained after debenzylation showed that, although reaction had taken place, no tocols were present, a result possibly connected with the unusual lability of the $C_{(5)}$ bromine atom.[7] 5-Bromotoluquinol likewise failed to give any identifiable products when treated with phytol under the same conditions, only a dark oil being formed.

Toluquinol 1-benzyl ether and diazotised sulphanilic acid gave a red azo-derivative which was reduced without isolation to the aminophenol and acetylated to give a low yield of 4-acetamido-5-acetoxy-2-benzyloxytoluene (II; R = CH_2Ph, R′ = Ac, X = NHAc), the structure of which was confirmed by an alternative synthesis. Cold alkaline hydrolysis of this product yielded 5-acetamidotoluquinol 1-benzyl ether (II; R = CH_2Ph, R′ = H, X = NHAc), which did not react with phytol under the usual conditions or when zinc chloride in boiling acetic acid was used.

Reaction of toluquinol 1-benzyl ether with phytol in decalin, zinc chloride being used as catalyst, gave, after hydrogenation, a poor yield of the expected mixture of 5- and 7-methyltocol. Reaction in benzene–formic acid yielded a cleaner product containing about 68% of an unseparable mixture of 5- and 7-methyltocol. Reaction of toluquinol 1-methyl ether with phytol in benzene–formic acid followed by demethylation gave a 45% yield of 5- and 7-methyltocol. As it was inseparable, this material was at first thought to be of no help in the preparation of 5-methyltocol. However, a concentrated

[4] Jacob, Sutcliffe, and Todd, *J.*, 1940, 327; cf. Aparicio and Waters, *J.*, 1952, 4666, for the dibenzoate.
[5] Clark, *Amer. Chem. J.*, 1892, **14**, 569.
[6] Green, Marcinkiewicz, and Watt, *J. Sci. Food Agric.*, 1955, **6**, 274.
[7] Green, McHale, Mamalis, and Marcinkiewicz, *J.*, 1959, 3374.

mixture of 5- and 7-methyltocol benzyl ethers behaved as did tocol benzyl ether [8] on distillation and paper-chromatography of the distillate showed that two reducing bands were present, the slower band being in the position expected for 5- and/or 7-methyltocol, the faster band moving to a position expected for a *C*-benzylmethyltocol. Whereas the slower band coupled with diazotised *o*-dianisidine, the fast band did not, indicating that the $C_{(5)}$ position was blocked and that this product was probably 5(7)-benzyl-7(5)-methyltocol. Cleavage and rearrangement might therefore have occurred at the high temperature of the distillation. Cleavage and intermolecular rearrangement of benzyl [9] and phenyl [10] ethers in the absence of catalyst has been reported.

Four products could clearly be obtained from a mixture of 5- and 7-methyltocol benzyl ether: 5-methyltocol benzyl ether could give 7-benzyl-5-methyltocol and 5-methyltocol, while 7-methyltocol benzyl ether could give 5-benzyl-7-methyltocol and 7-methyltocol. There was reason to suppose that the ratio of cleavage to rearrangement of the two benzyl ethers would be different, since, because of the considerably greater reactivity of position $C_{(5)}$ than of position $C_{(7)}$ in tocols, 5-methyltocol benzyl ether was less likely to rearrange and hence give preferentially 5-methyltocol, while the 7-methyl benzyl ether might give more of the rearrangement product, 5-benzyl-7-methyltocol. This assumption was supported by evidence [11] that radical attack may take place preferentially at positions reactive from polar considerations.

When a 70% concentrate of the monomethyltocol benzyl ethers was heated without solvent at 250°, appreciable cleavage and rearrangement occurred to give a product containing 15% of monomethyltocols and a similar amount of benzylmethyltocols: a cleaner product containing 28% of monomethyltocols resulted from reaction in tetradecane. The product was chromatographically separated into two components, the faster of which failed to couple with diazotised *o*-dianisidine, could not be nitrosated, and contained 71% of mixed benzylmethyltocols. Distillation afforded slightly impure benzylmethyltocol. The slower band after further chromatography afforded a small quantity of almost non-coupling yellow oil (assay 94%) and a residual oil which coupled strongly. Distillation of the former gave apparently 5-methyltocol. In replicate experiments it was extremely difficult to isolate the non-coupling 5-methyltocol even when the product was rebenzylated and again heated at 250°. The reason became clear with the development of a method for the determination of 5- and 7-methyltocols in the presence of one another, based on the assay of their nitrosation products.[12] The product of condensation of phytol with toluquinol 1-benzyl ether was then shown to contain 5- and 7-methyltocol in the ratio 1 : 2, a result very close to that observed from the reaction of toluquinol itself with phytol.[3] The condensation product of toluquinol 1-methyl ether with phytol similarly contained 38% of 5-methyl- and 62% of 7-methyl-tocol. In one experiment the relative proportions of the two tocols were little altered by thermal reaction. Since the condensation gave rise to 7-methyltocol as main product, and since successful alternative methods for the synthesis of 5-methyltocol had been developed,[13] this approach was abandoned.

The Table records the yields of crude tocols, formed by condensation of various toluquinols with phytol, as assayed by paper chromatography after removal of the protecting group.

The feature of these results is the effect of a $C_{(5)}$-substituent; in general, condensations with $C_{(5)}$-substituted toluquinols or toluquinol monoether give much lower yields of tocols than do toluquinols not substituted in this position (cf. expts. 5—8 and 10 with 1—4). 5-Substituted derivatives furnish considerably poorer yields than do the 6-substituted

[8] Mamalis, McHale, Green, and Marcinkiewicz, *J.*, 1958, 1850.
[9] Behagel and Freiensehner, *Ber.*, 1934, **67**, 1368.
[10] *Idem*, *Ber.*, 1935, **68**, 341.
[11] Augood, Hey, and Williams, *J.*, 1952, 2094; 1953, 44; Augood, Cadogan, Hey, and Williams, *J.*, 1953, 3412; Cadogan, Hey, and Williams, *J.*, 1954, 794.
[12] Marcinkiewicz and Green, *Analyst*, 1959, **84**, 304.
[13] McHale, Green, Marcinkiewicz, and Mamalis, following paper.

Condensation of phytol with toluquinols: yields of tocols derived by assay of crude product.

Expt.	Toluquinol (IV)	Yields (%) 5-methyl-	7-methyl-	8-methyl-
1	R = R′ = X = Y = H [a]	18	32	21
2	R = Me, R′ = X = Y = H	17	28	0
3	R = CH_2Ph, R′ = X = Y = H	24	44	0
4	R = X = Y = H, R′ = Me	0	22	14
5	R = R′ = Y = H, X = Br	0	0	0
6	R = CH_2Ph, R′ = Y = H, X = Br	0	0	0
7	R = CH_2Ph, R′ = Y = H, X = NHAc	0	0	0
8	R = R′ = YH, X = SMe [b]	6	0	19
9	R = R′ = XH, Y = SMe [b]	25	31	0
10	R = Me, R′ = Y = H, X = S·CH_2·CH_2·OH [b]	5	0	0
11	2,3-Dihydro-6-hydroxy-7-methylbenz-1,4-oxathiin-2-one [c]	0	0	22

[a] Ref. 3. [b] Ref. 13. [c] Ref. 7.

compounds (expts. 8 and 9). The free $C_{(5)}$ position appears to be so reactive that toluquinol 4-methyl ether yields more 7- than 8-methyltocol on reaction with phytol (expt. 4), the initial attack by phytol taking place at $C_{(5)}$ adjacent to the methoxyl group, rather than at $C_{(6)}$ adjacent to the hydroxyl: no reaction appears to take place at $C_{(3)}$. 2,3-Dihydro-6-hydroxy-7-methylbenz-1,4-oxathiin-2-one has been included since it is in effect a toluquinol 4-ether blocked at $C_{(5)}$.

Repetition of the reaction of pure toluquinol 4-benzoate with phytol as described by Jacob *et al.*[4] gave only one tocol, 8-methyltocol. This confirmed the structure of the 4-benzoate since if the product had been the 1-isomer or had been contaminated with it, both 5- and 7-methyltocol should have been found in the product. The report of Pendse and Karrer [2] that 7-methyltocol was obtained from this reaction must be attributed to the use of an impure sample of the 4-benzoate. In the same way, the structure of toluquinol 1-benzyl ether followed from the fact that only 5- and 7-methyltocol were obtained from its reaction with phytol. Conversion of 5-acetamidotoluquinol 1-benzyl ether into the known 5-bromotoluquinol dimethyl ether [14] by standard reactions confirmed the structure assigned earlier. Catalytic hydrogenation of 5-acetamidotoluquinol 1-benzyl ether afforded 5-acetamidotoluquinol (II; R = R′ = H, X = NHAc), which on methylation gave 5-acetamidotoluquinol dimethyl ether (II; R = R′ = Me, X = NHAc). Acid hydrolysis of the dimethyl ether gave the aminoquinol dimethyl ether (II; R = R′ = Me), X = NH_2), and the latter was converted by means of the Sandmeyer reaction into 5-bromotoluquinol dimethyl ether (II; R = R′ = Me, X = Br).

5-Acetamidotoluquinol dimethyl ether was also obtained by mild alkaline hydrolysis of 5-acetamido-5-acetoxy-2-methoxytoluene to 4-acetamido-5-hydroxy-2-methoxytoluene (II; R = Me, R′ = H, X = NHAc) followed by methylation.

It was also observed that nitration of toluquinol dimethyl ether gave an excellent yield of 5-nitrotoluquinol dimethyl ether (II; R = R′ = Me, X = NO_2), the structure of which was confirmed by reduction to the amine (II; R = R′ = Me, X = NH_2).

Experimental

All tocol assays and paper-chromatographic examinations were carried out as described by Green *et al.*[6]

Benzoylation of Toluquinol.—Toluquinol (50 g.) was benzoylated according to Jacob *et al.*[4], giving toluquinol dibenzoate (4·4 g.), m. p. 122°, toluquinol 4-benzoate (18·5 g.), m. p. 113—115°, and mixed monobenzoates (40 g.), m. p. 102—104°. Jacob *et al.* give m. p. 113—114° for the 4-benzoate and m. p. 122° for the dibenzoate, while Aparicio and Waters [4] give m. p. 124° for the latter.

5-Benzoyloxy-2-benzyloxy- and 2-Benzoyloxy-5-benzyloxy-toluene.—Toluquinol 4-benzoate (7·1 g.; m. p. 113—115°), benzyl bromide (5·2 ml.), potassium carbonate (9·1 g.), and acetone

[14] McHale, Mamalis, Green, and Marcinkiewicz, *J.*, 1958, 1600.

(100 ml.) were heated under reflux for 4 hr. and then cooled. Water was added, and the oil extracted into ether and washed with N-sodium hydroxide and with water. Removal of the solvent and crystallisation from light petroleum (b. p. 60—80°) gave needles (6·6 g.), m. p. 117—119°.

5-Benzoyloxy-2-benzyloxytoluene (A) when recrystallised had m. p. 118—119° (Found: C, 79·3; H, 5·9. $C_{21}H_{18}O_3$ requires C, 79·3; H, 5·7%). Distillation of the crystallisation mother-liquors afforded a pale yellow oil (2·4 g.), b. p. 190—205°/0·05 mm., m. p. 75—79°. After two crystallisations from light petroleum (b. p. 60—80°), needles of *2-benzoyloxy-5-benzyloxytoluene* (B), m. p. 87—89°, were obtained (Found: C, 79·0; H, 5·7%).

Toluquinol 4-Benzoate.—5-Benzoyloxy-2-benzyloxytoluene (1·0 g.) in ethanol (20 ml.) was shaken with hydrogen and palladised charcoal (10%) till uptake ceased (85 ml.). The white product (0·61 g.), m. p. 120—122° on crystallisation from ethanol–light petroleum (b. p. 60—80°) formed prismatic needles, m. p. 120—122°. The *trityl ether* separated from alcohol as needles, m. p. 138—139° (Found: C, 83·8; H, 5·6. $C_{33}H_{26}O_3$ requires C, 84·0; H, 5·6%).

Toluquinol 1-Benzoate.—2-Benzoyloxy-5-benzyloxytoluene (1·0 g.), partially dissolved in ethanol (40 ml.), was reduced catalytically as above; it gave a white *product* (0·65 g.), which after crystallisation from ethanol–light petroleum (b. p. 60—80°) formed needles, m. p. 145—146° (Found: C, 73·3; H, 5·6. $C_{14}H_{12}O_3$ requires C, 73·6; H, 5·3%).

Toluquinol 1-Benzyl Ether.—A suspension of 5-benzoyloxy-2-benzyloxytoluene (25·1 g.) in ethanol (230 ml.) was stirred under nitrogen at 60° while N-sodium hydroxide (157 ml.) was added during 5 min. After a further 2 hr. at 60° the mixture was cooled and acidified with concentrated hydrochloric acid (10 ml.), and most of the ethanol removed under reduced pressure. An oil separated which was extracted into ether, and washed thoroughly with aqueous sodium hydrogen carbonate and water; acidification of the alkaline solution gave benzoic acid (8·3 g.), m. p. 122°, while evaporation of the ethereal layer gave a cream solid (14·4 g.), m. p. 67—69°. *Toluquinol 1-benzyl ether* separated from ether–light petroleum (b. p. 40—60°) as needles, m. p. 70—71° (Found: C, 78·0; H, 6·7. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%).

Toluquinol 4-Benzyl Ether.—Similarly prepared from 2-benzoyloxy-5-benzyloxytoluene, the *4-benzyl ether* crystallised from ethyl acetate–light petroleum (b. p. 60—80°) in prisms, m. p. 85—86° (Found: C, 78·7; H, 6·6%).

Direct Preparation of 5-Benzoyloxy-2-benzyloxy- and 2-Benzoyloxy-5-benzyloxy-toluene from Toluquinol.—Benzoylation of toluquinol (78·6 g.) gave toluquinol dibenzoate (11·5 g.) and the mixed monobenzoates (87·4 g.). Benzylation of the latter afforded a product which on crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) yielded the 5-benzoyloxy-derivative (54·9 g.) as needles, m. p. 115—116°. Distillation of the evaporated mother-liquors gave the 2-benzoyloxy-derivative (b. p. 190—210°/0·2 mm.), crystallising from light petroleum (b. p. 60—80°) as needles (30·3 g.), m. p. 86—89°.

Benzylation of Toluquinol.—Toluquinol (6·2 g.), benzyl bromide (8·6 g.), potassium carbonate (6·9 g.), and acetone (25 ml.) were heated under reflux for 4 hr. Water was added, the oil extracted into ether, and the extracts washed with water and dried. The solvent was removed and the residual oil distilled, two fractions being collected: (i) b. p. 50—148°/0·02 mm. (1·2 g.), consisting of toluquinol (0·23 g.), m. p. 122—124°, and benzyl bromide; and (ii) an oil, b. p. 148—152°/0·02 mm. (4·6 g.), which partially solidified. An ethereal solution of the solid (1·1 g.) from the higher-boiling fraction was washed with N-sodium hydroxide and evaporated. Crystallisation yielded long soft white needles of *toluquinol dibenzyl ether*, m. p. 49—51° (Found: C, 82·4; H, 6·6. $C_{21}H_{20}O_2$ requires C, 82·7; H, 6·6%), the structure of which was confirmed by hydrogenation to toluquinol. The dark oil (3·0 g.) remaining after removal of the solid was treated with pyridine (15 ml.) and benzoyl chloride (2·0 g.), then heated on the steam-bath for 1 hr. The tan-coloured solid (2·7 g.) separated from light petroleum (b. p. 60—80°) as needles of 2-benzoyloxy-5-benzyloxytoluene, m. p. 78—89° (Found: C, 78·8; H, 5·6. Calc. for $C_{21}H_{18}O_3$: C, 79·3; H, 5·7%).

5-Bromotoluquinol 1-Benzyl Ether.—(*a*) Toluquinol 1-benzyl ether (2·1 g.) in chloroform (10 ml.; dry) was stirred at 5° while bromine (1·6 g.) in chloroform (10 ml.) was added rapidly. The mixture was immediately evaporated, the residue stirred with cold chloroform (5 ml.), and the solid collected (0·52 g.). Crystallisation from water containing a little ethanol afforded 5-bromotoluquinol, m. p. 181—183° undepressed on admixture with an authentic specimen.[14] The original chloroform mother-liquors were evaporated to afford a sticky brown solid (1·85 g.). Three crystallisations from light petroleum (b. p. 60—80°) yielded prismatic needles, m. p.

66·5—68°, of 5-*bromotoluquinol* 1-*benzyl ether* (Found: C, 57·3; H, 4·4; Br, 27·3. $C_{14}H_{13}O_2Br$ requires C, 57·3; H, 4·5; Br, 27·3%). Catalytic hydrogenation of a sample furnished 5-bromotoluquinol, m. p. 181—183°.

(*b*) Toluquinol 1-benzyl ether (6·4 g.), calcium carbonate (9·0 g.), and chloroform (90 ml.) were stirred at 5° while bromine (4·8 g.) in chloroform (30 ml.) was added during 15 min. After being left overnight, the mixture was filtered and the residue washed with chloroform; evaporation of the filtrate and crystallisation from light petroleum gave prismatic needles (7·8 g.), m. p. 65·5—67°.

4-*Acetamido*-5-*acetoxy*-2-*benzyloxytoluene*.—To a solution of sulphanilic acid (1·73 g.) and sodium carbonate (0·44 g.) in water (8 ml.) was added sodium nitrite (0·61 g.) in water (2·0 ml.). The mixture was poured on ice (10 g.) and concentrated hydrochloric acid (1·75 ml.) and left for 15 min. The diazonium solution was then added to an ice-cold solution of sodium hydroxide (1·25 g.) in water (5 ml.) containing toluquinol 1-benzyl ether (1·22 g.), set aside overnight, then stirred with sodium dithionite (2·1 g.) for 30 min. at room temperature. The oil which separated was extracted into ethyl acetate, the solvent removed, and the residue kept with acetic anhydride (5 ml.) and concentrated sulphuric acid (1 drop) for 3 hr. After the addition of water, the solid was collected and crystallised from aqueous ethanol, the *product* separating as long white needles, m. p. 180—183°. Recrystallisation gave needles, m. p. 181° (Found: C, 68·7; H, 6·3; N, 4·6. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1; N, 4·5%).

5-*Acetamidotoluquinol* 1-*Benzyl Ether*.—The diacetyl derivative (0·6 g.), ethanol (12 ml.), and N-sodium hydroxide (4·8 ml.) were kept at room temperature for 1 hr., the mixture was then acidified with concentrated hydrochloric acid, water was added, and the solid *product* collected (0·5 g.) and crystallised from aqueous ethanol, giving white needles, m. p. 168—169° (Found: 70·8; H, 6·2; N, 5·3. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·3; N, 5·2%).

Attempted Reactions with Phytol.—(*a*) 5-Bromotoluquinol 1-benzyl ether (2·9 g.), phytol (3·0 g.), anhydrous formic acid (15 ml.), and benzene (15 ml.) were heated under reflux for 4 hr., the mixture becoming very dark. The benzene layer was separated, washed with N-sodium hydroxide and water, dried, and evaporated. The dark oil was shaken with hydrogen and palladised charcoal (10%) until uptake ceased. Paper-chromatographic examination failed to indicate any tocol products.

(*b*) 5-Bromotoluquinol (2·0 g.), phytol (3·0 g.), formic acid (15 ml.), and benzene (15 ml.) were heated under reflux for 3 hr. Separation and evaporation of the benzene layer left a dark oil that did not contain tocol products.

(*c*) 5-Acetamidotoluquinol 1-benzyl ether (150 mg.), phytol (170 mg.), benzene (1·5 ml.), and formic acid (1·5 ml.) were heated under reflux for 5 hr. The pale benzene layer was separated, washed with N-sodium hydroxide and water, and evaporated. The crude oil (170 mg.), after catalytic hydrogenation, was examined paper-chromatographically; no tocol products were identified. Acidification of the alkaline washings yielded unchanged material.

5- *and* 7-*Methyltocol*.—(*a*) Toluquinol 1-benzyl ether (5·0 g.), phytol (7·0 g.), anhydrous zinc chloride (3·3 g.), and decalin (90 ml.) were stirred at 140—150° for 3 hr. The hot supernatant solution was decanted off, and the residual gum, after being washed once with decalin (20 ml.), was rejected; the combined decalin solutions, when cooled, deposited white solid (0·45 g.). Crystallisation from benzene–light petroleum (b. p. 40—60°) gave toluquinol, m. p. and mixed m. p. 126—127°. The decalin solution was evaporated to give a dark oil (10·6 g.) which was taken up in ethanol (50 ml.) and ethyl acetate (20 ml.) and shaken with hydrogen and palladised charcoal (10%). When hydrogen uptake ceased (450 ml.), the mixture was worked up to give an oil (7·5 g.), which was assayed by paper chromatography. Three reducing bands were observed, one on the origin (12%), one in the position expected for 5- and 7-methyltocol (34%), and a fast running band (11%) which did not couple with diazotised *o*-dianisidine. This is probably due to a $C_{(5)}$-substituted tocol of higher molecular weight; the overall yield of 5- and 7-methyltocols was 27%.

(*b*) Toluquinol 1-benzyl ether (1·1 g.), phytol (1·5 g.), formic acid (12 ml.), and benzene (12 ml.) were heated under reflux for 3 hr. The benzene layer was separated, washed with N-sodium hydroxide and water, and evaporated to give an oil which was hydrogenated in ethyl acetate (25 ml.). Working up afforded a pale brown oil (2·45 g.), which was shown to contain 5- and 7-methyltocol (assay 57%, overall yield 68%); distillation of this gave a dark yellow oil, b. p. 210—220°/0·03 mm. (assay 73% of 5- and 7-methyltocol). Very little fast-running material was obtained by this method.

5-Benzoyloxy-2-methoxy- and 2-Benzoyloxy-5-methoxy-toluene.—Mixed toluquinol monobenzoates (11·4 g.), methyl iodide (28 g.), potassium carbonate (13·8 g.), and acetone (40 ml.) were stirred under reflux for 3 hr. Water was added and the oil extracted into ethyl acetate, washed with N-sodium hydroxide and water, and dried. After removal of the solvent the residue was crystallised from light petroleum (b. p. 60—80°) giving buff crystals (5·6 g.), m. p 71—79°, a second crop (3·5 g.), m. p. 50—56°, and a third crop (1·6 g.), m. p. 46—50°. Fractional crystallisation from light petroleum (b. p. 60—80°) finally gave two pure products: *5-benzoyloxy-2-methoxytoluene* separated as prisms (3·6 g.), m. p. 88—89° (Found: C, 74·6; H, 6·0. $C_{15}H_{14}O_3$ requires C, 74·5; H, 5·8%), while *2-benzoyloxy-5-methoxytoluene* formed needles (2·9 g.), m. p. 55—57° (Found: C, 74·4; H, 5·6%). The 5-benzoyloxy-derivative was also prepared by methylation of toluquinol 4-benzoate (11·2 g.), giving the methyl ether (9·9 g.), m. p. and mixed m. p. 88—89°.

Toluquinol 1-Methyl Ether.—Alkaline hydrolysis of 5-benzoyloxy-2-methoxytoluene, as described for the corresponding benzyl ether, and crystallisation from light petroleum (b. p. 40—60°) gave needles, m. p. 44—46° (Bamberger [15] gives m. p. 46—46·5°). Toluquinol 4-methyl ether, similarly prepared from the isomeric benzoate, formed needles, m. p. 70—71°, from light petroleum (b. p. 40—60°) (lit.,[15] m. p. 70·5—71·5°).

5- and 7-Methyltocol from Toluquinol 1-Methyl Ether.—The methyl ether (1·3 g.), phytol (3·7 ml.), benzene (15 ml.), and formic acid (15 ml.) were heated under reflux for 4 hr. The upper layer was separated, the lower layer extracted with benzene, and the combined benzene solutions washed with N-sodium hydroxide and with water. Evaporation of the solvent left a brown oil (4·15 g.), which was heated with hydrogen bromide in acetic acid (42 ml.; 22%) and concentrated hydrochloric acid (4 ml.) for 4 hr. Working up yielded a 48% concentrate (3·4 g.) containing both 5- and 7-methyltocol the overall yield being 45%).

5- and 7-Methyltocol Benzyl Ethers.—The mixed tocols (2·47 g., 73% concentrate), benzyl bromide (1·6 ml.), and acetone (50 ml.) were shaken with sodium hydroxide solution (3·6 ml.; 36% w/v) for 2 hr. Water was added and the oil isolated with ether, washed with water, and dried. After removal of solvent and excess of benzyl bromide, the oil, now non-reducing, was distilled in a short-path still as a yellow oil, b. p. 210° (bath)/0·02 mm. The distillate was now reducing. On catalytic reduction of a sample of the distilled benzyl ether, the concentration of 5- and 7-methyltocol was found to be 71%.

Thermal Reaction of 5- and 7-Methyltocol Benzyl Ethers.—The benzyl ether mixture (1·55 g.; 71%) in tetradecane (35 ml.) was heated under gentle reflux for 1 hr. The solvent was removed under vacuum, and the dark residual oil (1·1 g.) examined by paper chromatography. Two reducing bands were present, a slower band containing 5- and 7-methyltocol (amounting to 28% of the total material) and a faster band containing benzylmethyltocols (*ca.* 22% of total). The two reducing products were separated by chromatography on zinc carbonate–Hyflo Super-cel.

(*a*) The faster brown oil was free from 5- and 7-methyltocol, did not couple with diazotised *o*-dianisidine, and gave an assay of *ca.* 71%. The exact concentration was uncertain since the requisite spectrophotometric factor was assumed to be the same as for 5,7-dimethyltocol. Distillation gave the mixed benzylmethyltocols as an orange-yellow oil, b. p. 180° (bath)/10^{-2} mm. (Found: C, 82·1; H, 10·5. Calc. for $C_{34}H_{52}O_2$: C, 82·8; H, 10·6%), $\nu_{max.}$ 3509 w, 2907 vs, 1460 s, 1376 m, 1344 w, 1323 m, 1225 w, and 1157 m cm.$^{-1}$.

(*b*) The slower brown oil was rechromatographed to give a dark yellow oil (69 mg.) which was almost non-coupling with diazotised *o*-dianisidine; assay showed 92% of 5-methyltocol. Distillation afforded a pale yellow oil, b. p. 130° (bath)/5 × 10^{-4} mm. (Found: C, 81·6; H, 12·1. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%).

Proportions of 5- and 7-Methyltocol in Phytol Condensation Products.—The proportions were determined as described by Green and Marcinkiewicz,[12] involving the preparation and quantitative separation of the nitrosated tocols. Toluquinol 1-benzyl ether with phytol gave 5-methyltocol (35%) and 7-methyltocol (67%), while toluquinol 1-methyl ether gave 5-methyltocol (38%) and 7-methyltocol (62%). In one experiment, after thermal treatment of the mixed tocol benzyl ethers, the tocol band comprised 5-methyltocol (34%) and 7-methyltocol (66%).

5-Acetamidotoluquinol.—5-Acetamidotoluquinol 1-benzyl ether (1·0 g.) in alcohol (30 ml.) was shaken with hydrogen and palladised charcoal (10%) till uptake ceased. The catalyst and solvent were removed and the *product* was crystallised from ethyl acetate–light petroleum

[15] Bamberger, *Annalen*, 1912, **390**, 174.

(b. p. 60—80°), forming small white prisms (0·55 g.), m. p. 175—177° (Found: C, 59·6; H, 6·2; N, 8·0. $C_9H_{11}O_3N$ requires C, 59·7; H, 6·1; N, 7·8%). The *dibenzyl ether* separated from aqueous alcohol in fine white needles, m. p. 116—117° (Found: C, 76·3; H, 6·1; N, 4·2. $C_{23}H_{23}O_3N$ requires C, 76·5; H, 6·4; N, 3·9%).

5-Acetamidotoluquinol Dimethyl Ether.—5-Acetamidotoluquinol (0·9 g.), methyl iodide (2·5 g.), potassium carbonate (1·4 g.), and acetone (15 ml.) were heated under reflux for 5 hr. After removal of most of the solvent, addition of water caused separation of a solid which was taken up in ethyl acetate, washed with N-sodium hydroxide and water, and dried. Evaporation of solvent and crystallisation from aqueous alcohol gave flat white needles, m. p. 164—166° (Found: C, 63·2; H, 7·0; N, 6·7. $C_{11}H_{15}O_3N$ requires C, 63·2; H, 7·2; N, 6·7%).

5-Aminotoluquinol Dimethyl Ether.—The acetamido-derivative (1·5 g.), concentrated hydrochloric acid (10 ml.), acetic acid (10 ml.), and water (10 ml.) were heated under reflux for 2 hr. The mixture was concentrated and the product crystallised from alcohol–ethyl acetate, the *amine hydrochloride* separating as white needles, m. p. 207—208° (decomp.) (Found: C, 53·5; H, 7·0; N, 7·0. $C_9H_{14}O_2NCl$ requires C, 53·1; H, 6·9; N, 6·9%). The *base* formed plates, m. p. 112—113°, from aqueous alcohol (Found: C, 64·2; H, 7·8; N, 8·1. $C_9H_{13}O_2N$ requires C, 64·7; H, 7·9; N, 8·4%).

5-Bromotoluquinol Dimethyl Ether.—5-Aminotoluquinol dimethyl ether (1·95 g.), hydrobromic acid (3·5 ml.; 48%), and water (1·5 ml.) were stirred at 0° while sodium nitrite (0·82 g.) in water (1·5 ml.) was slowly added. The diazonium solution was added in portions to cuprous bromide (1·5 g.) in hydrobromic acid (1·0 ml.; 48%) heated on the steam-bath. After completion of the addition the product was isolated by steam-distillation, the distillate was extracted with ethyl acetate, and the extracts were dried and evaporated. The residue was crystallised from aqueous alcohol, 5-bromotoluquinol dimethyl ether separating as prisms (1·65 g.), m. p. 92—93°, not depressed on admixture with an authentic specimen [15] possessing an identical infrared spectrum (Found: C, 46·9; H, 4·5; Br, 35·0. Calc. for $C_9H_{11}O_2Br$: C, 46·7; H, 4·8; Br, 34·6%).

4-Acetamido-5-acetoxy-2-methoxytoluene.—This *amide* was prepared from toluquinol 1-methyl ether, as previously described for the 2-benzyloxytoluene derivative, and formed needles, m. p. 145—147°, from alcohol (Found: C, 61·0; H, 6·5; N, 5·7. $C_{12}H_{15}O_4N$ requires C, 60·8; H, 6·4; N, 5·9%). Hydrolysis with cold aqueous alcoholic sodium hydroxide afforded *5-acetamidotoluquinol 1-methyl ether*, which crystallised from aqueous alcohol as white needles, m. p. 161° (Found: C, 61·4; H, 6·7; N, 7·2. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·8; N, 7·2%). Methylation of this product yielded 5-acetamidotoluquinol dimethyl ether, m. p. 164—166°, identical with the product described above.

5-Nitrotoluquinol Dimethyl Ether.—Toluquinol dimethyl ether (1·5 g.) in glacial acetic acid (10 ml.) was stirred at 20° and nitric acid (0·7 ml.; *d* 1·42) was added during 15 min. After a further hour, the mixture was poured into water, and the product crystallised from alcohol, the *nitro-compound* forming glistening yellow needles, m. p. 117—118° (Found: C, 54·6; H, 5·9; N, 7·4. $C_9H_{11}O_4N$ requires C, 54·8; H, 5·6; N, 7·1%). Catalytic reduction (palladised charcoal) gave 5-aminotoluquinol dimethyl ether, m. p. 112—113°, identical with the product already described.

We thank Mr. C. Watson for technical assistance.

WALTON OAKS EXPERIMENTAL STATION,
VITAMINS, LTD., TADWORTH, SURREY.

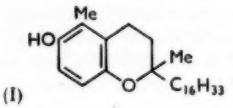
[*Received, March 2nd,* 1959.]

679. *Tocopherols. Part IV.*[1] *Synthesis of 5-Methyltocol.*

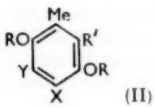
By D. McHale, P. Mamalis, S. Marcinkiewicz, and J. Green.

Racemic 5-methyltocol has been synthesised by an unambiguous route.

During paper-chromatographic analysis of the tocopherol fraction from wheat-germ oil, Brown [2] observed a spot that reduced Emmerie and Engel's reagent,[3] but failed to couple with diazotised *o*-dianisidine. Eggitt *et al.*, by reason of its chromatographic behaviour [4] and a number of other reactions,[5] suggested that the spot was due to 5-methyltocol (I) and used the name ε-tocopherol for the substance.



(I)



(II)

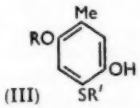
Karrer and Fritzsche [6] condensed toluquinol with phytol and obtained a mixture which was later shown by Marcinkiewicz, McHale, Mamalis, and Green [7] to contain 5-, 7-, and 8-methyltocol. Karrer and Dutta [8] tried to prevent the formation of these isomeric mixtures by condensing phytol with a methylthio-toluquinol, the methylthio-group being removed subsequently by Raney nickel. Two routes were used for the preparation of the methylthio-compounds but both led to a mixture of the same two isomers. One of these isomers was shown to be 5-methylthiotoluquinol (II; R = R′ = Y = H, X = SMe), which when condensed with phytol and desulphurised gave the expected mixture of 5- and 8-methyltocol. The other isomer when similarly treated gave a methyltocol whose *p*-phenylazobenzoate melted at 46—47°. A mixture with a specimen of the *p*-phenylazobenzoate that Stern, Robeson, Weisler, and Baxter [9] obtained from natural 8-methyltocol (δ-tocopherol) melted without depression, although their compound melted several degrees lower. This led Karrer and Dutta to assume that their synthetic compound was 8-methyltocol and that the methylthio-compound, from which it was derived, was 3-methylthiotoluquinol (II; R = X = Y = H, R′ = SMe). By using the paper-chromatographic technique [10] to identify the products, our repetition of this work showed that the " so-called " 8-methyltocol, synthesised by Karrer and Dutta, was in fact a mixture of 5- and 7-methyltocol and, therefore, that the methylthio-compound was 6-methylthiotoluquinol (II; R = R′ = X = H, Y = SMe) and not 3-methylthiotoluquinol as supposed.

Because of the difficulty in separating mixtures of monomethyltocols none of these earlier routes was suitable for the preparation of pure 5-methyltocol. An alternative approach was therefore considered, of using a type of blocked compound that, if the route were successful, would give only one isomer. Karrer and Dutta attempted to prevent formation of mixtures in the synthesis of the monomethyltocols by condensing phytol with a bismethylthiotoluquinol; although they obtained the bismethylthiomethyltocol they were unable to convert it into the monomethyltocol. It was shown in Part III [1] that when the 1-hydroxy-group of toluquinol was blocked by a benzyl group no condensation occurred at position 6, only 5- and 7-methyltocol being formed. Therefore, it was thought that

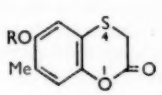
[1] Part III, preceding paper.
[2] Brown, *Biochem. J.*, 1952, **51**, 237; 1952, **52**, 523.
[3] Emmerie and Engel, *Rec. Trav. chim.*, 1938, **57**, 1351.
[4] Eggitt and Ward, *J. Sci. Food Agric.*, 1953, **4**, 569.
[5] Eggitt and Norris, *ibid.*, 1955, **6**, 689; 1956, **7**, 493.
[6] Karrer and Fritzsche, *Helv. Chim. Acta*, 1939, **22**, 260.
[7] Marcinkiewicz, McHale, Mamalis, and Green, *J.*, 1959, 3377.
[8] Karrer and Dutta, *Helv. Chim. Acta*, 1948, **31**, 2080.
[9] Stern, Robeson, Weisler, and Baxter, *J. Amer. Chem. Soc.*, 1947, **69**, 869.
[10] Green, Marcinkiewicz, and Watt, *J. Sci. Food Agric.*, 1955, **5**, 274.

condensation of phytol with a 5-alkylthiotoluquinol 1-alkyl ether (III) would lead to 5-methyltocol. If the deactivating influence of the ether group was insufficient to prevent condensation occurring *ortho* to it, the product, an alkoxyphenol, would be separable by chromatography from the other condensation product, a substituted methyltocol ether.

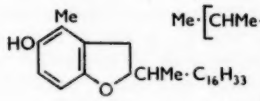
Methylation of 2,3-dihydro-6-hydroxy-7-methylbenz-1,4-oxathiin-2-one (IV; R = H)[11] gave the 6-methoxy-compound (IV; R = Me), which was reduced by lithium aluminium hydride to 5-2′-hydroxyethylthiotoluquinol 1-methyl ether (III; R = H, R′ = CH_2·CH_2·OH). The condensation of this compound with phytol gave only a low yield, most of the methyl ether being recovered, and all attempts to improve the yield failed. The product, after desulphurisation with Raney nickel and demethylation with hydrobromic acid in acetic acid, gave an oil, which after chromatography and molecular distillation assayed as 100% of 5-methyltocol (the ε-tocopherol spectrophotometric factor of



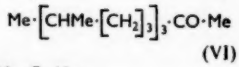
(III)



(IV)



(V)



(VI)

96 being used [5]). The paper-chromatographic properties were similar to those of natural ε-tocopherol but the compound appeared to be heterogeneous in that part of the band coupled with diazotised *o*-dianisidine.[12] As the simple 5-hydroxy-4-methylcoumarans, unsubstituted at position 6, couple with diazotised *o*-dianisidine [15] some cyclisation to the coumaran (V) might have occurred.

Alternative approaches were then considered and 5-methyltocol was eventually synthesised by a route similar to that which McHale *et al.*[13] used for 7-methyltocol. 2,3-Dimethylquinol (II; R = X = Y = H, R′ = Me) was prepared from 2,3-dimethylphenol by Smith and Austin's method [14] and methylated. The resulting dimethyl ether (II; X = Y = H, R = R′ = Me), on bromination with *N*-bromosuccinimide, gave 3-bromomethyltoluquinol dimethyl ether (II; X = Y = H, R = Me, R′ = CH_2Br) together with some 2,3-bisbromomethylquinol dimethyl ether. The bromination had to be carried out under strictly anhydrous conditions and the dimethylquinol to be free from monoether, or nuclear bromination occurred. All attempts to obtain 3-2′-hydroxyethyltoluquinol dimethyl ether (II; X = Y = H, R = Me, R′ = CH_2·CH_2·OH) from the bromomethyl compound by a Grignard reaction with formaldehyde failed, the main product being 3,3′,6,6′-tetramethoxy-2,2′-dimethylbibenzyl. The bromomethyl compound was converted into 3-cyanomethyltoluquinol dimethyl ether (II; X = Y = H, R = Me, R′ = CH_2·CN), which on alkaline hydrolysis gave 3,6-dimethoxy-2-methylphenylacetic acid (II; X = Y = H, R = Me, R′ = CH_2·CO_2H). Although lithium aluminium hydride reduced this compound to 3-2′-hydroxyethyltoluquinol dimethyl ether, the yield was low, as an insoluble complex separated before reduction. Unchanged acid was obtained when the residue was acidified. The yield of hydroxyethyl compound on reduction of the methyl ester (II; X = Y = H, R = Me, R′ = CH_2·CO_2Me) was almost quantitative. With phosphorus tribromide the hydroxyethyl compound gave 3-2′-bromoethyltoluquinol dimethyl ether (II; X = Y = H, R = Me, R′ = CH_2·CH_2Br); the Grignard derivative of this ether was treated with ketone (VI), derived from phytol by ozonolysis.[13] No attempt was made to separate the products, demethylation and cyclisation being carried out on the crude mixture. A crude concentrate containing 14% of 5-methyltocol was obtained, which after adsorption on alumina and molecular distillation afforded an oil that gave correct analyses for 5-methyltocol and from which the *p*-phenylazobenzoate was prepared.

[11] Green, McHale, Mamalis, and Marcinkiewicz, *J.*, 1959, 3374.
[12] Weisler, Robeson, and Baxter, *Analyt. Chem.*, 1947, **19**, 906.
[13] McHale, Mamalis, Green, and Marcinkiewicz, *J.*, 1958, 1600.
[14] Smith and Austin, *J. Amer. Chem. Soc.*, 1942, **64**, 530.
[15] Green, McHale, Marcinkiewicz, and Mamalis, following paper.

Experimental

2,3-*Dihydro-6-methoxy-7-methylbenz*-1,4-*oxathiin*-2-*one* (IV; R = Me).—The 6-hydroxy-compound [11] (IV; R = H) (5·6 g.), methyl iodide (9·5 g.), anhydrous potassium carbonate (2 g.), and acetone (20 ml.) were refluxed for 6 hr. The product was obtained *via* ether extraction. Crystallisation from 95% ethanol gave the *methyl ether* (3·6 g.), m. p. 83—84° (Found: C, 57·1; H, 4·8; S, 14·9. $C_{10}H_{10}O_3S$ requires C, 57·2; H, 4·8; S, 15·3%).

5-2′-*Hydroxyethylthiotoluquinol* 1-*Methyl Ether* (III; R = Me, R′ = CH_2·CH_2·OH).—To a stirred suspension of lithium aluminium hydride (0·4 g.) in dry ether was added, dropwise, the 6-methoxybenzoxathiinone (1·5 g.) in dry ether. After decomposition of the excess of lithium aluminium hydride by ether saturated with water, the product was poured on a mixture of ice and concentrated hydrochloric acid and extracted with ether. The extract was washed with water, and dried and evaporated. Crystallisation from light petroleum (b. p. 80—100°) gave the *hydroxyethylthio-compound* (1·2 g.), m. p. 82—83° (Found: C, 56·0; H, 6·4; S, 14·8. $C_{10}H_{14}O_3S$ requires C, 56·0; H, 6·6; S, 15·0%).

Condensation of **5-2′-*Hydroxyethylthiotoluquinol* 1-*Methyl Ether with Phytol***.—The hydroxyethylthio-compound (0·54 g.), phytol (0·75 g.), anhydrous zinc chloride (0·1 g.), and acetic acid (20 ml.) were refluxed for 6 hr. The product was diluted with light petroleum (b. p. 40—60°), and washed successively with water, N-sodium hydroxide, and water. Acidification of the alkaline extract gave the hydroxyethylthio-compound (0·2 g.). The light-petroleum extract was evaporated, and an ethanolic solution (20 ml.) of the oil (0·55 g.) refluxed for 6 hr. with Raney nickel (1 g.). After filtration and evaporation the residue was refluxed for 3 hr. with hydrobromic acid (2·5 g.) in acetic acid (7·5 ml.). The product was diluted with light petroleum (b. p. 40—60°), and washed with water, followed by saturated aqueous sodium hydrogen carbonate, and evaporated to a brown oil (0·5 g.) which contained 4·5% of 5-methyltocol (by assay).[10] This concentrate was purified by adsorption from light petroleum (b. p. 40—60°) on alumina (Peter Spence type "O"; 3 g.). After development of the column with light petroleum–benzene the 5-methyltocol was eluted with ether. Evaporation and distillation [at 160° (bath)/10^{-3} mm.] gave a pale yellow oil (9 mg.) which gave an assay of 100% of 5-methyltocol. When the chromatogram was sprayed successively with 5% aqueous sodium carbonate and diazotised *o*-dianisidine [12] part of the tocol zone coupled to give a purple dye.

2 : 3-*Dimethylquinol Dimethyl Ether* (II; X = Y = H, R = R′ = Me).—2,3-Dimethylquinol [14] (20 g.), methyl iodide (40 g.), anhydrous potassium carbonate (40 g.), and acetone (150 ml.) were stirred under reflux for 16 hr. The product was isolated by steam-distillation and extracted into ether. After removal of the monomethyl ether by extraction with N-sodium hydroxide, evaporation and crystallisation from aqueous ethanol gave the *dimethyl ether* (12 g.), m. p. 78—79° (Found: C, 72·6; H, 6·7. $C_{10}H_{14}O_2$ requires C, 72·3; H, 6·7%). Acidification of the alkaline extract and crystallisation from light petroleum (b. p. 60—80°) gave the *monomethyl ether* (2·2 g.), m. p. 98—99° (Found: C, 71·2; H, 8·0. $C_9H_{12}O_2$ requires C, 71·0; H, 8·0%).

3-*Bromomethyltoluquinol Dimethyl Ether* (II; X = Y = H, R = Me, R′ = CH_2Br).—2,3-Dimethylquinol dimethyl ether (11 g.), *N*-bromosuccinimide (12 g.), benzoyl peroxide (0·1 g.), and dry carbon tetrachloride (200 ml.) were refluxed for 1 hr. A second portion of benzoyl peroxide (0·1 g.) was then added and refluxing continued until no *N*-bromosuccinimide remained. After cooling, the succinimide was filtered off and the filtrate evaporated to an oil which was taken up in light petroleum (b. p. 40—60°) and allowed to crystallise. The solid (A) was filtered off and the filtrate evaporated and distilled, giving the *bromomethyl compound* (9·9 g.), b. p. 102°/0·2 mm., m. p. 51—52° (Found: C, 48·4; H, 5·4; Br, 33·4. $C_{10}H_{13}O_2Br$ requires C, 49·0; H, 5·4; Br, 32·6%).

Recrystallisation of solid (A) from light petroleum (b. p. 60—80°) gave **2,3-*bisbromomethylquinol dimethyl ether*** (1·9 g.), m. p. 149° (Found: C, 37·6; H, 3·5; Br, 49·1. $C_{10}H_{12}O_2Br_2$ requires C, 37·1; H, 3·7; Br, 49·4%).

Reaction of* 2,3-*Dimethylquinol Dimethyl Ether with* N-*Bromosuccinimide in the Presence of* 2,3-*Dimethylquinol Monomethyl Ether.—2,3-Dimethylquinol dimethyl ether (containing traces of monomethyl ether) (11 g.), *N*-bromosuccinimide (12 g.), benzoyl peroxide (0·1 g.), and dry carbon tetrachloride (200 ml.) were refluxed for 30 min., by which time all the *N*-bromosuccinimide was converted into succinimide and hydrobromic acid was being evolved. Filtration, evaporation, and distillation gave an oil (9·5 g.), b. p. 88—90°/0·05 mm., m. p. 41—42° [from light petroleum (b. p. 40—60°) at −10°]. This compound was assumed to be **5-*bromo*-2,3-*dimethylquinol dimethyl ether*** (Found: C, 49·7; H, 5·4; Br, 32·5. $C_{10}H_{13}O_2Br$ requires C, 49·0; H, 5·4; Br, 32·3%).

3,3',6,6'-*Tetramethoxy*-2,2'-*dimethylbibenzyl*.—3-Bromomethyltoluquinol dimethyl ether (5 g.) in dry ether (25 ml.) was added slowly, with stirring, to magnesium turnings (0·6 g.) activated with a crystal of iodine and gently heated on a steam-bath. After 1·5 hr. the suspension was cooled to 0°, and formaldehyde [from paraformaldehyde (1·5 g.)] was introduced above the surface of the ether. The resulting mixture was hydrolysed by ice-cold 25% sulphuric acid (10 ml.). The solid was filtered off and crystallised from benzene to give the *bibenzyl compound* (3 g.), m. p. 181—183° (Found: C, 72·9; H. 7·9. $C_{20}H_{26}O_4$ requires C, 72·7; H, 7·9%). Evaporation of the original ether solution gave a small amount of viscous oil.

3-Cyanomethyltoluquinol Dimethyl Ether (II; X = Y = H, R = Me, R' = CH_2·CN).—A solution of 3-bromomethyltoluquinol dimethyl ether (10 g.) in dioxan (100 ml.) was added to a stirred solution of sodium cyanide (5·0 g.) in water (5 ml.), heated on a steam-bath, during 1·5 hr. The mixture was heated for a further 3 hr., diluted with water, and extracted with ether. After being washed free from dioxan, the ether extract was dried and evaporated. The solid (5·2 g.), when crystallised from light petroleum (b. p. 60—80°) gave the *cyanomethyl compound* (4·2 g.), m. p. 63—64° (Found: C, 69·1; H, 7·1; N, 7·3. $C_{11}H_{13}O_2N$ requires C, 69·2; H, 6·9; N, 7·3%).

3,6-*Dimethoxy*-2-*methylphenylacetic Acid* (II; X = Y = H, R = Me, R' = CH_2·CO_2H).—The cyanomethyl compound (4·8 g.) in ethanol (40 ml.) was refluxed with potassium hydroxide (6 g.) in water (12 ml.) for *ca.* 36 hr. Evaporation of the ethanol gave a solid that was taken up in water and extracted with ether. Acidification of the aqueous layer gave the *acetic acid* (3·2 g.), m. p. 144—146° [from light petroleum (b. p. 80—100°)] (Found: C, 63·0; H, 7·1. $C_{11}H_{14}O_4$ requires C, 62·8; H, 6·7%).

The methyl ester (prepared by use of diazomethane in ether and crystallised from methanol–water) had m. p. 64° (Found: C, 63·7; H, 6·9. Calc. for $C_{12}H_{16}O_4$: C, 64·3; H, 7·2%).

Reduction by Lithium Aluminium Hydride of the Acetic Acid.—To a stirred suspension of lithium aluminium hydride (1·2 g.) in ether (30 ml.) was added, dropwise, a suspension of the acetic acid (4 g.) in ether (30 ml.). The mixture was then refluxed for 30 min., cooled, and hydrolysed by ether saturated with water. The inorganic solid was filtered off and washed with ether; the filtrate and washings were combined and evaporated. Crystallisation from light petroleum (b. p. 80—100°) gave **3-2'-*hydroxyethyltoluquinol dimethyl ether*** (II; X = Y = H, R = Me, R' = CH_2·CH_2·OH) (1·6 g.), m. p. 82—83° (Found: C, 67·4; H, 8·4. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%).

Acidification of the inorganic residue and extraction with ether gave the unchanged acetic acid (2 g.), m. p. 144—146°.

Reduction by Lithium Aluminium Hydride of Methyl **3,6-*Dimethoxy*-2-*methylphenylacetate*.**—The ester was reduced by lithium aluminium hydride as already described for the acid. The hydroxyethyl compound (7·5 g. from 9·9 g.), m. p. 82—83°, was obtained.

3-2'-*Bromoethyltoluquinol Dimethyl Ether* (II; X = Y = H, R = Me, R' = CH_2·CH_2Br).—Phosphorus tribromide (3 g.) in light petroleum (10 ml.; b. p. 80—100°) was added slowly to a stirred solution of the hydroxyethyl compound (2·7 g.) in light petroleum (50 ml.; b. p. 80—100°) at 50°. After 2 hr. the mixture was cooled, hydrolysed by water (10 ml.), and decanted from the small amount of oil present. The organic layer was washed successively with water, saturated aqueous sodium hydrogen carbonate, and water, and evaporated. Crystallisation from methanol gave the *bromoethyl compound* (1·2 g.), m. p. 65—66° (Found: C, 51·2; H, 6·0; Br, 30·0. $C_{11}H_{15}O_2Br$ requires C, 51·0; H, 5·8; Br, 30·8%).

5-*Methyltocol* (I).—The bromoethyl compound (1·3 g.) and ethyl iodide (0·8 g.) in dry ether were added slowly to magnesium turnings (0·24 g.) activated by a crystal of iodine, and the whole was refluxed for 4—5 hr., then cooled to 0°. The ketone (VI) [13] (2·7 g.) was added dropwise and the mixture refluxed for a further 2 hr., cooled, and hydrolysed by dilute hydrochloric acid. Evaporation of the ether layer yielded an oil which was refluxed for 8 hr. with hydrobromic acid (5 g.) in acetic acid (50 ml.). The product was diluted with light petroleum (50 ml.; b. p. 40—60°) and washed successively with water, saturated aqueous sodium hydrogen carbonate, dilute hydrochloric acid, and water. Evaporation yielded a pale brown oil (3·1 g.) which contained 14% of 5-methyltocol (the ε-tocopherol spectrophotometric factor of 96 being used [5]). This oil was adsorbed from light petroleum (b. p. 40—60°) on to alumina (Peter Spence type " O "; 50 g.), which contained a small quantity of alumina previously treated with sodium fluorescein in methanol and activated at 150° for 1 hr. After development with benzene the band due to the tocol was detected by its quenching of the fluorescence under ultraviolet light.

The column was cut and the tocol extracted with ether. Evaporation gave a brown viscous oil (0·4 g.) which contained 63% of 5-methyltocol. Molecular distillation [at 140° (bath)/10^{-3} mm.] gave *5-methyltocol* as a pale yellow oil (Found: C, 80·0; H, 11·5. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%); $\lambda_{max.}$ 296 mμ ($E^{1\%}_{1\,cm.}$ 82·4), $\lambda_{min.}$ 258 mμ in ethanol; $\nu_{max.}$ 3440 m., 2915 vs, 1460 s, 1380 s, 1340 m, 1310 w, 1285 w, 1245 s, 1155 m, 1100 w, 1065 w, 1025 w, 911 w, 883 w, 862 w, and 807 m $cm.^{-1}$ (liquid film).

5-Methyltocol p-*Phenylazobenzoate*.—5-Methyltocol (0·1 g.), in dry ethylene chloride (5 ml.) containing pyridine (0·4 ml.), was heated under reflux with *p*-phenylazobenzoyl chloride (0·2 g.) in dry ethylene chloride (5 ml.) for 2 hr. Water (2 ml.) was added and after 1 hr. the product was taken up in light petroleum (b. p. 40—60°) and washed with dilute hydrochloric acid and water. The organic layer was filtered from the insoluble *p*-phenylazobenzoic acid and evaporated. The oil was redissolved in light petroleum, and the solution filtered; evaporation and crystallisation from propan-2-ol, gave needles, m. p. 69—70° (Found: C, 78·5; H, 9·0; N, 4·8. $C_{40}H_{54}O_3N_2$ requires C, 78·7; H, 8·8; N, 4·6%).

The authors are grateful to Mr. P. R. Watt for the infrared spectra and to Mr. P. Ashurst for technical assistance.

WALTON OAKS EXPERIMENTAL STATION,
VITAMINS, LTD., TADWORTH, SURREY. [*Received, March 2nd,* 1959.]

---

680. *Tocopherols. Part V.*[1] *Structural Studies on ε- and ζ-Tocopherol.*

By J. GREEN, D. MCHALE, S. MARCINKIEWICZ, P. MAMALIS, and P. R. WATT.

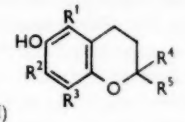
Natural ε-tocopherol has been shown to differ from synthetic 5-methyltocol, with which it had previously been identified. Spectroscopical, chromatographical, synthetical, and degradative evidence is presented confirming the nature of the synthetic compound. ε-Tocopherol would appear to be a 5,8-disubstituted chromanol, related to the tocols, but perhaps with altered substitution at $C_{(2)}$. Natural ζ-tocopherol from wheat bran is not identical with 5,7-dimethyltocol, which structure had been given it, but appears to be the trisubstituted representative in the same series as ε-tocopherol. The ζ-tocopherol that occurs in rice, however, is apparently identical with authentic 5,7-dimethyltocol.

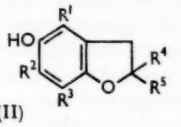
WHEN McHale, Mamalis, Marcinkiewicz, and Green's synthetic 5-methyltocol [1] was converted into a nitroso-derivative by Quaife's method [2] and this compound compared chromatographically with the nitroso-derivative of natural ε-tocopherol [3] the R_f values of the two compounds were different. Since ε-tocopherol has been identified with 5-methyltocol, it was necessary to compare in detail the chemistry of the two compounds.

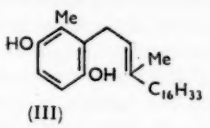
Eggitt and Ward [4] considered that ε-tocopherol was 5-methyltocol because, on partition chromatography (a system sensitive to molecular-weight differences), it migrated almost identically with 8-methyltocol. This was also the view of Green, Marcinkiewicz, and Watt,[5] who found that the substance migrated in a two-dimensional adsorption-partition chromatographic system to the same position as 7-methyltocol. Eggitt and Norris [6] compared the behaviour of ε-tocopherol with that of other tocopherols and concluded that ε-tocopherol was probably 5-methyltocol, from the failure of the former to enter coupling reactions, its formation of a nitroso-derivative whose ultraviolet and visible spectra were closely similar to those of the nitroso-derivative of 5,8-dimethyltocol, the nearly

[1] Part IV, preceding paper.
[2] Quaife, *J. Biol. Chem.*, 1948, **175**, 605.
[3] Marcinkiewicz and Green, *Analyst*, 1959, **84**, 304.
[4] Eggitt and Ward, *J. Sci. Food Agric.*, 1953, **4**, 569.
[5] Green, Marcinkiewicz, and Watt, *ibid.*, 1955, **6**, 274.
[6] Eggitt and Norris, *ibid.*, p. 689.

quantitative formation of a " tocopheroxide " (now known to be a hemiketal, not an oxide [7]), whose ultraviolet spectrum (with $\lambda_{max.}$ at 265 mμ) was identical with the " tocopheroxide " from 5,8-dimethyltocol, and a number of other oxidation reactions.


(I)


(II)


(III)

The identity of the synthetic material with 5-methyltocol (I; $R^1 = R^4 = Me$, $R^2 = R^3 = H$, $R^5 = C_{16}H_{33}$), on the other hand, appeared to rest securely on its method of synthesis, which was parallel to the synthesis of α-tocopherol [8] and of 7-methyltocol,[9] its ultraviolet and infrared spectra, its behaviour towards the *o*-dianisidine and ferric chloride–bipyridyl reagents, and its two-dimensional paper-chromatographic behaviour. The only step in its synthesis with any degree of uncertainty appeared to be the chroman ring closure. If the unsaturated compound (III) is an intermediate in the cyclisation, there is a possibility that, by anti-Markovnikov addition, a coumaran would result. The nature of this type of ring closure and the possibility of coumaran formation was discussed by Karrer, Fritzsche, Ringier, and Salomon [10] and by Smith.[11] The formation of a coumaran (II; $R^1 = Me$, $R^2 = R^3 = R^4 = H$, $R^5 = CHMe{\cdot}C_{16}H_{33}$) would presume that cyclisation did not follow the course shown by Smith and his co-workers [12] to operate with more fully methylated model compounds; nevertheless, this was a possibility that was considered during the earlier structural studies.

ε-Tocopherol was isolated from wheat-bran oil by Ward's method [13] and distilled in a micro-molecular still as a yellow oil. Paper-chromatographic analysis showed that it contained only one reducing substance, corresponding in migration to the material described by Eggitt and Ward. Since the quantity obtained by the laborious procedure was small and its purity was uncertain (although oxidation with ferric chloride indicated that the preparation was of about 90% purity) no combustion analyses were attempted and the available material was used in a comparative study of the chemistry of ε-tocopherol and the synthetic 5-methyltocol of McHale *et al.*, pending further attempts to prepare crystalline derivatives.

Coupling Evidence.—Neither the synthetic material nor natural ε-tocopherol coupled with diazotised *o*-dianisidine, which reaction is given by tocols unsubstituted at $C_{(5)}$. The inactivity at $C_{(7)}$ in these 6-chromanols towards coupling is even more marked than the well-known Mills–Nixon effect in the corresponding 6-tetralols and has been described in some detail.[13a] The position of coupling in 5-coumaranols has not been described and it could not be assumed that, as in the corresponding 5-indanols, coupling would occur only at $C_{(6)}$. Indeed, Arnold and McCool [14] have shown that nitration takes place at $C_{(4)}$ in certain coumarans. Some model compounds were synthesised and tested with the *o*-dianisidine reagent. 4-Methylcoumaran-5-ol (II; $R^1 = Me$, $R^2 = R^3 = R^4 = R^5 = H$) and 2,4,7-trimethylcoumaran-5-ol (II; $R^1 = R^3 = R^4 = Me$, $R^2 = R^5 = H$) coupled with the reagent to give a purple dye, whereas 6-methylcoumaran-5-ol (II; $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Me$) did not. This indication that coumaranols couple at $C_{(6)}$ is strong evidence for the chromanol structure of the synthetic preparation in which the

[7] Martius and Eilingsfeld, *Annalen*, 1957, **607**, 159.
[8] Smith and Miller, *J. Amer. Chem. Soc.*, 1942, **64**, 440.
[9] McHale, Mamalis, Green, and Marcinkiewicz, *J.*, 1958, 1600.
[10] Karrer, Fritzsche, Ringier, and Salomon, *Helv. Chim. Acta*, 1938, **21**, 520.
[11] Smith, *Chem. Rev.*, 1940, **27**, 287.
[12] (*a*) Smith, Ungnade, Hoehn, and Wawzonek, *J. Org. Chem.*, 1929, **4**, 305; (*b*) *idem, ibid.*, p. 311; (*c*) Smith, Ungnade, Stevens, and Christman, *J. Amer. Chem. Soc.*, 1939, **61**, 2615.
[13] Ward, *Brit. J. Nutrition*, 1958, **12**, 226.
[13a] Green and Marcinkiewicz, *Analyst*, 1959, **84**, 297.
[14] Arnold and McCool, *J. Amer. Chem. Soc.*, 1942, **64**, 1315.

position of the methyl group is known (leaving the possibility of a $C_{(6)}$-substituted coumaranol structure for natural ε-tocopherol still open).

Spectroscopic Studies.—The ultraviolet spectra of synthetic 5-methyltocol, ε-tocopherol and β-tocopherol were almost identical, all having $\lambda_{max.}$ at 296 mμ and $\lambda_{min.}$ at 258 mμ. The infrared spectra of the three compounds were very similar (Fig. 1). Rosenkrantz,[15] discussing the spectra of α-, γ-, and δ-tocopherol and some related compounds, attributed bands in the 7μ (1430 cm.$^{-1}$) region to the vibration of C–H linkages and methyl groups. In this region, the spectra of 5,8-dimethyltocol and ε-tocopherol each show three bands, respectively, at 1458, 1410, 1373 cm.$^{-1}$, and 1448, 1415, 1377 cm.$^{-1}$. The spectrum of synthetic 5-methyltocol, however, has bands at 1476, 1458, and 1373 cm.$^{-1}$, and resembles more closely the spectra of tocol (bands at 1479, 1455, and 1376 cm.$^{-1}$) and 8-methyltocol (bands at 1463 and 1382 cm.$^{-1}$). The spectra of three model chromanols and four model coumaranols were compared in the 1110—1250 cm.$^{-1}$ region with those of the tocopherols (Table 1). These were 2,5,8-trimethyl-, 2,5,7,8-tetramethyl- and 2,2,5,7,8-pentamethylchroman-6-ol (I; $R^1 = R^3 = R^4 = Me$, $R^2 = R^5 = H$; $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = H$; $R^1 = R^2 = R^3 = R^4 = R^5 = Me$, respectively), 2,4,6,7-tetramethylcoumaran-5-ol (II; $R^1 = R^2 = R^3 = R^4 = Me$, R = H), and 4-methyl-, 6-methyl-, and 2,4,7-trimethyl-coumaran-5-ol. Rosenkrantz has stated that the strong band that appears near 8·6 μ (1162 cm.$^{-1}$) in the spectra of α-, γ-, and δ-tocopherol is characteristic of the tocol type of structure. This band is indeed present in the spectra of all the tocopherols examined by us, of ε-tocopherol, and of the synthetic 5-methyltocol. It is also present in the spectra of the three 2-substituted chromanols, but is absent from those of the two 2-substituted coumaranols. In the spectra of the two coumaranols unsubstituted at $C_{(2)}$, it is apparently replaced by two bands. Rosenkrantz has also discussed the 8 μ (1250 cm.$^{-1}$) band, which probably results from the C–O vibration of the phenolic hydroxyl, and concludes that increased substitution by methyl groups in tocopherols results in a progressive shift, towards shorter wavelengths. When all the spectra are compared, however, this is seen to be a simplification and the position of methyl substitution is more important than the number of methyl groups in determining the wavelength shift. Thus, in the spectrum of 7-methyltocol, the band appears at 1240 cm.$^{-1}$ and is very weak. The band at 1246 cm.$^{-1}$ in the spectrum of synthetic 5-methyltocol may, perhaps, resemble the band in the analogous, *ortho*-substituted 7-methyltocol, whereas the position of the band at 1231 cm.$^{-1}$ in ε-tocopherol seems to place it more nearly in the category of dimethyltocols. The total infrared evidence indicates that ε-tocopherol may be a chromanol, disubstituted in the aromatic nucleus in a similar way to β-tocopherol.

TABLE 1. *Infrared bands in the* 1110—1250 *cm.*$^{-1}$ *region of tocopherols, chromanols, and coumaranols.*

Compound	ν (cm.$^{-1}$)	ν (cm.$^{-1}$)	Compound	ν (cm.$^{-1}$)	ν (cm.$^{-1}$)
Tocol	1218	1152	2,2,5,7,8-Pentamethylchroman-6-ol	1222	1166
7-Methyltocol	1240	1178	4-Methylcoumaran-5-ol	1222	1191, 1138
8-Methyltocol	1218	1152	6-Methylcoumaran-5-ol	1265	1187, 1159
5,8-Dimethyltocol	1229	1158	2,4,7-Trimethylcoumaran-5-ol	1208	None
7,8-Dimethyltocol	1221	1155	2,4,6,7-Tetramethylcoumaran-5-ol	1231	None
5,7-Dimethyltocol	1223	1162	Synthetic 5-methyltocol	1246	1155
5,7,8-Trimethyltocol	1266, 1210	1159	ε-Tocopherol	1231	1164
2,5,8-Trimethylchroman-6-ol	1230	1148			
2,5,7,8-Tetramethylchroman-6-ol	1258	1149			

Chromatographic Evidence.—Brown [16] and Eggitt and Ward [4] both remarked that the migration of ε-tocopherol on paper partition chromatograms appeared to be faster than that of 8-methyltocol. The difference is slight and can be overlooked unless the chromatograms are carefully constructed. We therefore compared carefully the R_F values of

[15] Rosenkrantz, *J. Biol. Chem.*, 1948, **173**, 439.
[16] Brown, *Biochem. J.*, 1952, **51**, 237.

synthetic 5-methyltocol, 7-methyltocol, 8-methyltocol, and ε-tocopherol by the descending method, the stationary phase being liquid paraffin and the mobile phase 75% v/v ethanol. After 4 hours' migration, the R_F values were respectively 0·52, 0·49, 0·52, and 0·62. In the same system, tocol had an R_F value of 0·67 and this would indicate that if ε-tocopherol is a chromanol, it probably has a lower molecular weight than the monomethyltocols.

Nitrosation Evidence.—Tocols that are unsubstituted at $C_{(5)}$ or $C_{(7)}$ can be nitrosated under Quaife's conditions.[2] It has been shown by Marcinkiewicz and Green[3] that sub-milligram quantities of almost pure nitrosotocopherols can be obtained by nitrosation at high dilution followed by a two-step paper-chromatographic separation. Attempts to prepare the nitrosotocopherols on a larger scale failed, owing to rapid oxidation of the nitroso-compounds. This kind of difficulty in the preparation of *o*-nitrosophenols may be noted in the work of Cronheim [17] who prepared 52 *o*-nitrosophenols in amounts sufficient for light-absorption studies but was unable to give any analytical results. We have repeated some of Cronheim's preparations and confirmed the minute yields of even the simplest *o*-nitrosophenols under normal preparative conditions. The nitrosotocopherols were therefore characterised by their ultraviolet and infrared spectra.

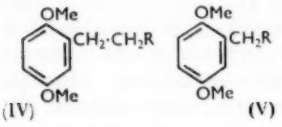
The light-absorption data in the visible and near ultraviolet on the nitroso-derivatives of 5,8-dimethyltocol, 7,8-dimethyltocol, and 8-methyltocol obeyed [2,6] Cronheim's rules for *o*-nitrosophenols. These rules state that (1) the wavelength of minimum absorption increases with the number of substituents in the benzene ring, and (2) the wavelength of maximum absorption depends on the distance between the hydroxy-group and the nearest substituent other than the nitroso-group itself. The nitroso-derivatives of 7-methyltocol and the synthetic 5-methyltocol preparation obeyed Chronheim's rules, both having $\lambda_{max.}$ at 413—415 mμ and $\lambda_{min.}$ at 338—340 mμ. We have, however, confirmed the previous findings [6] that the nitroso-derivative of ε-tocopherol did not have $\lambda_{min.}$ at 340 mμ (as would be expected if ε-tocopherol were a monomethylphenol) but at 358 mμ, identical with $\lambda_{min.}$ of nitroso-5,8-dimethyltocol.

When the nitroso-derivatives of the synthetic 5-methyltocol and ε-tocopherol were compared in the paper-chromatographic system of Marcinkiewicz and Green (93% v/v ethanol against liquid paraffin), the R_F values were quite different, being 0·21 and 0·60, respectively, compared with 0·31 for 7-methyl-5-nitrosotocol. In this system, the R_F values of 7,8-dimethyl-5-nitrosotocol and 5,8-dimethyl-7-nitrosotocol are 0·19 and 0·42, respectively. 8-Methyltocol gave two nitroso-derivatives,[3] with R_F values of 0·79 and 0·48, which, on the basis of their relative proportion formed during nitrosation (*ca.* 1 : 3) and their infrared spectra, are considered to be 8-methyl-7-nitroso- and 5-nitroso-tocol, respectively. The infrared spectra of the 7-nitroso-derivatives of the methylated tocols contained a band of medium strength near 1720 $cm.^{-1}$ (presumably due to carbonyl stretching vibration), which was absent from or very weak in the spectra of the 5-nitroso-derivatives. Comparison of the relative order of the R_F values suggested that the nitroso-derivative from the synthetic 5-methyltocol migrated anomalously. Tocol also gave two nitroso-derivatives which in spite of their lower molecular weights, migrated more slowly than the nitroso-derivatives of 8-methyltocol, having R_F values of 0·59 and 0·27. In view of these anomalous results, and since the constitution of synthetic tocol itself had been based on assumptions derived from the work of Smith *et al.*,[11,12] it seemed desirable at this stage to correlate the structure of tocol and synthetic 5-methyltocol. Tocol was therefore synthesised by a route parallel to that used for 5-methyltocol by McHale *et al.*, and then converted directly into a compound identical with the latter.

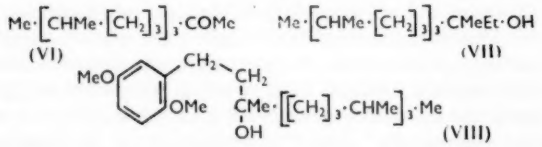
New Syntheses of Tocol and 5-Methyltocol.—The intermediate required for the new synthesis of tocol was 2-2′-hydroxyethylquinol dimethyl ether (IV; R = OH). Toluquinol dimethyl ether and *N*-bromosuccinimide readily gave 2-bromomethylquinol dimethyl ether (V; R = Br). Several attempts were made to prepare the Grignard reagent from

[17] Cronheim, *J. Org. Chem.*, 1945, **12**, 20.

this, but the only isolable product was 1,2-bis-(2,5-dimethoxyphenyl)ethane. 2-Chloromethylquinol dimethyl ether (V; R = Cl) had previously been prepared[18] from the hydroxymethyl compound (V; R = OH) by treatment with phosphorus pentachloride. We were able to prepare it in low yield, admixed with a nuclear chlorinated substance,


(IV)

(V)


(VI)

(VII)

(VIII)

probably 5-chlorotoluquinol dimethyl ether, by the chlorination of toluquinol dimethyl ether with 1,3-dichloro-5,5-dimethylhydantoin in carbon tetrachloride in the presence of benzoyl peroxide. In view of the poor yield, the chloro-compound was not further investigated. Attempts were then made to replace the bromine atom in the bromomethyl ether by the cyano-group. Although this atom was sufficiently labile to be replaced by methoxyl merely by heating in methanol for a short time, reaction with sodium cyanide in aqueous dioxan was slow. After 5 hr. under reflux, a poor yield of 2-cyanomethylquinol dimethyl ether (V; R = CN) was obtained and this could be smoothly hydrolysed to the known homogentisic acid dimethyl ether[18,19] (V; R = CO_2H). Reduction with lithium aluminium hydride afforded 2-2′-hydroxyethylquinol dimethyl ether, a compound eventually prepared in better yield from 2-bromoquinol.[20] Methylation of the latter gave the dimethyl ether,[21] and reaction of its Grignard reagent with ethylene oxide afforded 2-2′-hydroxyethylquinol dimethyl ether, identical with the product by the first route. Replacement of the hydroxyl group by bromine was best accomplished with phosphorus tribromide in ether containing a trace of pyridine.

The Grignard reagent from 2-2′-bromoethylquinol dimethyl ether, prepared by the entrainment technique with ethyl iodide, and 6,10,14-trimethylpentadecan-2-one (VI) gave two products, a lower-boiling oil, probably 3,7,11,15-tetramethylhexadecan-3-ol (VII), and 1-(2,5-dimethoxyphenyl)-3,7,11,15-tetramethylhexadecan-3-ol (VIII). The latter, when heated with hydrogen bromide in acetic acid, gave an oil, which, after chromatography and molecular distillation, gave pure tocol identical with a specimen prepared by Mamalis *et al.*[22]

The direct introduction of a methyl group at $C_{(5)}$ in tocol is considered difficult.[22,23] Chloromethylation and hydroxymethylation gave unidentified products or unchanged material. This is due to the slow substitution in the unmethylated tocol nucleus compared with the much faster reaction for monosubstituted intermediates. By hydroxymethylation at room temperature with only a trace of alkali, followed by reduction, we were able to prepare, in about 50% yield, a monomethyltocol identical in all respects with the 5-methyltocol of McHale *et al.*

Degradation of Tocol.—The chromanol structure of the synthetic 5-methyltocol was confirmed by oxidative degradations similar to those carried out by Fernholz[24] on α-tocopherol. Tocol itself was used since it was available in larger amounts and its structural relation to the synthetic specimen of McHale *et al.* had been proved. Fernholz used (+)-α-tocopherol and it was thought advisable to compare the degradative products of tocol with those of synthetic (±)-α-tocopherol, in order to avoid possible stereochemical effects. In fact the degradation products of (+)- and (±)-α-tocopherol were identical.

[18] Baumann and Frankel, *Z. physiol. Chem.*, 1895, **20**, 221.
[19] Abbott and Smith, *J. Biol. Chem.*, 1949, 179, 365.
[20] Sarauw, *Annalen*, 1881, **209**, 99.
[21] Noelting and Werner, *Ber.*, 1890, **23**, 3250.
[22] Mamalis, McHale, Green, and Marcinkiewicz, *J.*, 1958, 1850.
[23] Pendse and Karrer, *Helv. Chim. Acta*, 1957, **40**, 1837.
[24] Fernholz, *J. Amer. Chem. Soc.*, 1938, **60**, 700.

Tocol gave the same C_{21}-lactone as α-tocopherol, and the *S*-benzylisothiuronium salts of the parent hydroxy-acids had the same m. p. and mixed m. p. This degradation provided proof of the authentic chromanol structures of tocol and 5-methyltocol.

Chloromethylations and Hydroxymethylations. The Structure of Natural ζ-Tocopherol.—The structure of the synthetic 5-methyltocol was finally confirmed by its conversion into 5,8-dimethyltocol (β-tocopherol) and 5,7,8-trimethyltocol (α-tocopherol). Chloromethylation for 2 hr. at room temperature, followed by reduction,[25] gave 28·5% of β-tocopherol and 26·4% of α-tocopherol. The identity of the β-tocopherol was confirmed by its chromatographic isolation, and conversion into a nitroso-derivative having the same ultraviolet spectrum and R_F value as authentic nitroso-β-tocopherol. The entry of the chloromethyl group *meta* to the hydroxy-group is remarkable and recalls substitutions in 1-substituted 2-naphthols. 5,7-Dimethyltocol could not be detected in the product, indicating either non-formation of a 7-chloromethyl derivative or, alternatively its very rapid conversion into a 7,8-bischloromethyl compound (giving α-tocopherol on reduction). The latter is unlikely since 7-methyltocol under similar conditions gave only 5,7-dimethyltocol, and 8-methyltocol only 5,8-dimethyltocol, showing that the chloromethyl group is strongly deactivating towards a second substitution. In contrast, if 7-methyltocol is chloromethylated in the presence of a reducing agent *in situ* such as stannous chloride, some α-tocopherol is produced.[26] After chloromethylation for 5 hr. and reduction, synthetic 5-methyltocol gave α-tocopherol in 53·5% yield. Isolation on a zinc carbonate–Hyflo Super-cel column, followed by molecular distillation, gave pure α-tocopherol.

Hydroxymethylation of 5-methyltocol and reduction gave only unidentified reducing products. Under slightly different conditions,[27] 7-methyltocol gave 7·8% of 5,7-dimethyltocol (81% unchanged) after 1 hr., and 8-methyltocol gave 47·4% of 5,8-dimethyltocol (40% unchanged) after 30 min. 7,8-Dimethyltocol could not be detected in any of the products. These experiments emphasise the lack of reactivity at $C_{(7)}$ towards the reagent (*meta*-substitution at $C_{(8)}$ is not possible in the Lederer–Manasse reaction).

ε-Tocopherol was chloromethylated under reducing conditions by Eggitt and Norris, who found that the product contained no α-tocopherol but a substance that they identified chromatographically as 5,7-dimethyltocol. It was clear to us that ε-tocopherol could not yield 5,7-dimethyltocol and that the chloromethylation product must have been another substance, chromatographically very similar. Since the naturally-occurring ζ-tocopherol, which is found with ε-tocopherol in the bran fraction of wheat, has previously been identified[5] with 5,7-dimethyltocol, we re-investigated the structures of the two compounds. ζ-Tocopherol was isolated,[5,26] from the lipid fraction of wheat bran, palm oil,* and unpolished rice. ε-Tocopherol was chloromethylated and reduced to give an 18% yield of a material that corresponded to the product described by Eggitt and Norris. This substance, synthetic 5,7-dimethyltocol, and the three specimens of ζ-tocopherol were compared chromatographically by the 4-hr. descending method. The R_F values of the synthetic specimen and of the specimen from rice were identical (0·28). The specimens of ζ-tocopherol from wheat and palm oil had R_F values equal to 0·36, identical with the R_F value of the chloromethylation product from ε-tocopherol. In contrast to the negative result with synthetic 5-methyltocol, hydroxymethylation of ε-tocopherol, followed by reduction, gave a product containing 21% of a substance chromatographically identical with the ζ-tocopherol of wheat. It is clear that neither the ε-tocopherol nor the ζ-tocopherol from wheat is a tocol. The former appears to be a disubstituted (probably dimethyl) chromanol, perhaps with altered substitution at $C_{(2)}$, although the possibility that it has the alternative 6,7-disubstituted coumaranol structure cannot be ruled out. The ζ-tocopherol in wheat is almost certainly the trisubstituted representative in the same series as

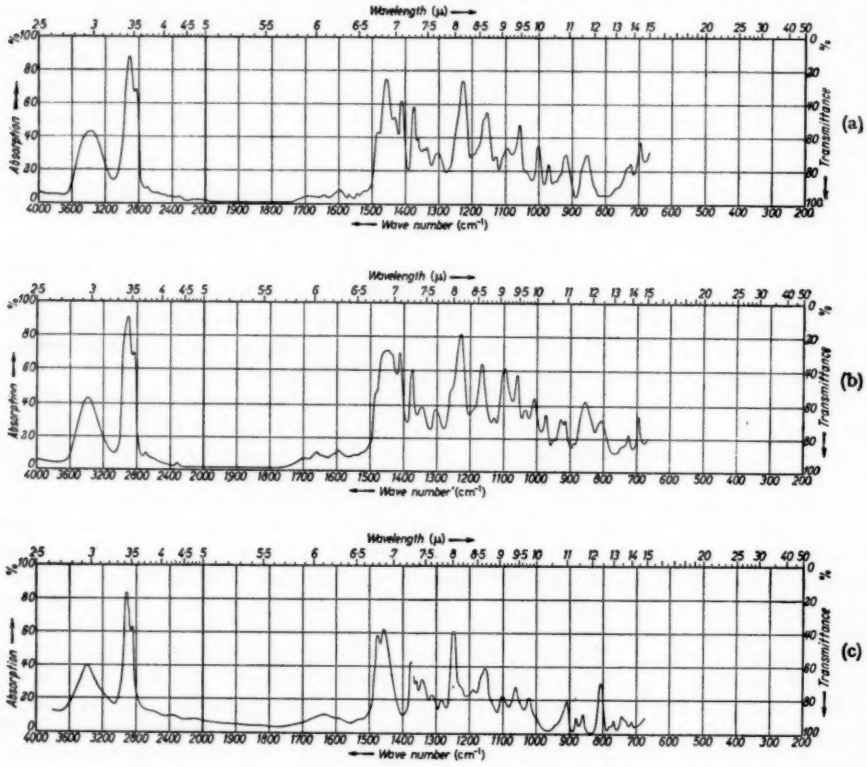
* We are indebted to Dr. R. J. Ward for the palm-oil preparation.

[25] B.P. 629,649, B.P. 639,011.
[26] Green and Marcinkiewicz, *Nature*, 1956, **176**, 86.
[27] B.P. 676,853.

ε-tocopherol. Further evidence for this was obtained by chloromethylating and reducing samples of synthetic 5,7-dimethyltocol and of ζ-tocopherol from wheat bran. The former gave α-tocopherol in 36% yield, whereas the latter gave no α-tocopherol or other identifiable product. The ζ-tocopherol that has been discovered in rice,[26] however, is apparently identical with 5,7-dimethyltocol. Thus, two different naturally-occurring substances, distinguishable from each other only with great difficulty, have both been called ζ-tocopherol. The problem of identity is of some importance from the point of view of animal nutrition.

In the course of this work, the identity of η-tocopherol with 7-methyltocol was confirmed by infrared and nitrosation studies.

Infrared spectra of (a) *β-tocopherol,* (b) *ε-tocopherol, and* (c) *synthetic 5-methyltocol.*



Experimental

Ultraviolet light absorption was measured with a Uvispek spectrophotometer. Infrared spectra were measured with a Grubb-Parsons DB 1/S4 spectrometer fitted with a sodium chloride prism: oils were measured as liquid films, and solids by the potassium bromide disc technique. Pressures cited for molecular distillations are Pirani-gauge measurements. Tocopherol analyses are by the method of Green *et al.*[5]

ε-Tocopherol.—This was obtained by Ward's method.[13] The product from 80 g. of wheat-bran oil when distilled [140° (bath)/5 × 10^{-3} mm.] gave 37 mg. of a pale yellow oil, which was chromatographically pure; $\lambda_{max.}$ 296 mμ, $\lambda_{min.}$ 258 mμ in ethanol; $\nu_{max.}$ 3390m, 2907vs, 1451vs, 1410vs, 1374s, 1229vs, 1164s, 1095s, 1059s, and 857m cm.$^{-1}$.

Chromatography of Tocols and Tocopherols.—The substances (20 μg. of each) were run side

by side on sheets of Whatman No. 1 paper by Eggitt and Ward's descending method.[4] R_F values, measured after 4 hr., for tocol, 5-, 7-, 8-methyltocol, and ε-tocopherol were, respectively, 0·67, 0·52, 0·49, 0·52, and 0·62.

Nitroso-derivatives.—The nitroso-derivatives were prepared by nitrosation of each tocopherol (500 μg.) as previously described [3] and purified chromatographically by separation on sheets of Whatman No. 1 paper impregnated with zinc carbonate. The yellow bands were eluted with ether, and the solutions filtered and evaporated at low temperature to give the nitroso-derivatives as bright yellow oils. Table 2 gives their ultraviolet-absorption maxima, R_F values (93% v/v ethanol as mobile phase), and main infrared absorption bands.

TABLE 2. *Physical data for nitroso-derivatives.*

Derivative	$\lambda_{max.}$ (mμ)	$\lambda_{min.}$ (mμ)	R_F	ν (cm.$^{-1}$)				
5(or 7)-Nitrosotocol *	405—410	326	0·59	2924vs	1732vw	1529m	1460s	1262m
7(or 5)-Nitrosotocol *	404	330—335	0·27	2924vs	—	1529m	1460s	—
5-Nitroso-7-methyltocol	415	358	0·31	2895vs	—	1528m	1456s	1262m
7-Nitroso-5-methyltocol	413	338	0·21	2907vs	1728w	1528m	1458s	1264m
5-Nitroso-8-methyltocol	405	340	0·48	2915vs	—	1519m	1458s	1261m
7-Nitroso-8-methyltocol	405	340	0·79	2907vs	1722w	1522m	1460s	1261m
Nitroso-ε-tocopherol	410	358	0·60	2915vs	1732w	1522m	1456s	1272m
5-Nitroso-7,8-dimethyltocol	415	355	0·19	2907vs	—	1522m	1452s	1261m
7-Nitroso-5,8-dimethyltocol	410	358	0·42	2907vs	1721w	1522m	1451s	1272m

* Structures uncertain. One is the 5- and the other the 7-nitroso-derivative.

4-*Methylcoumaran-5-ol* (II; $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Me$).—3-2′-Hydroxyethyltoluquinol dimethyl ether [1] (0·8 g.), hydrobromic acid (5 g.), and acetic acid (15 ml) were refluxed for 6 hr. The product was diluted with ether, and the extract washed successively with water, saturated aqueous sodium hydrogen carbonate, and water. Evaporation gave a black oil which was refluxed for 3 hr. with anhydrous potassium carbonate (2 g.) and acetone (10 ml.). The product was taken up in ether, washed free from acetone with water, and extracted with N-sodium hydroxide. The alkaline extract was acidified and extracted with ether. Evaporation gave a black oil (0·25 g.) which tended to crystallise. Vacuum sublimation [130° (bath)/0·04 mm.] gave the *coumaranol*, m. p. 111—112°, from water (Found: C, 71·9; H, 6·4. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%).

5-*Hydroxy*-2,4,7-*trimethylbenzofuran*.—To a stirred solution of sodium ethoxide [from sodium (0·56 g.) and ethanol (30 ml.)] containing ethyl acetoacetate (3·6 g.) at room temperature was added 2,5-dimethylbenzoquinone (3·3 g.) in ethanol (100 ml.) during 1·5 hr. The solution was kept overnight and poured on ice (250 g.) and concentrated hydrochloric acid (10 ml.), giving a tar from which the product was isolated by steam-distillation. The *benzofuran* separated as long white needles (0·25 g.), m. p. 133—134°, from aqueous ethanol (Found: C, 74·7; H, 6·8. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·9%).

2,4,7-*Trimethylcoumaran-5-ol* (II; $R^1 = R^3 = R^4 = Me$, $R^2 = R^5 = H$).—The benzofuran (0·5 g.) in ethanol (15 ml.) was shaken with hydrogen and palladised charcoal (10%) until uptake ceased (*ca.* 5 hr.; 65 ml. absorbed). Removal of catalyst and concentration gave white needles (0·33 g.), m. p. 85—87°, and a second crop (0·10 g.), m. p. 83—86°. Two recrystallisations from light petroleum (b. p. 40—60°) yielded the *coumaranol*, m. p. 97—99° (Found: C, 74·4; H, 8·0. $C_{11}H_{14}O_2$ requires C, 74·2; H, 8·0%).

5-2′-*Bromoethyltoluquinol*.—5-2′-Hydroxyethyltoluquinol dimethyl ether [3] (4·5 g.), hydrobromic acid (25 g.), and acetic acid (75 ml.) were refluxed for 6 hr. The product was diluted with ether, and the ethereal solution washed successively with water, saturated aqueous sodium hydrogen carbonate, and water. Evaporation and crystallisation from benzene gave the *quinol* as needles (2·1 g.), m. p. 156—157° (Found: C, 47·5; H, 5·1; Br, 33·8. $C_9H_{11}O_2Br$ requires C, 46·8; H, 4·8; Br, 34·6%).

6-*Methylcoumaran-5-ol* (II; $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Me$).—5-2′-Bromoethyltoluquinol (0·8 g.), anhydrous potassium carbonate (3·5 g.), and acetone (25 ml.) were refluxed for 1 hr. An ethereal solution of the product was washed with water and dried. Evaporation and crystallisation from benzene–light petroleum (b. p. 40—60°) gave the *coumaranol* (0·25 g.), m. p. 135—136° (Found: C, 71·5; H, 6·8. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%).

6-*Hydroxy*-2,5,8-*trimethylchroman*-4-*one*.—2,5-Dimethylquinol (14·0 g.), ethyl acetoacetate (18·0 g.), and ethanol (10 ml.) were stirred at 0—5° while phosphoric oxide (30 g.) was added in

small portions. The temperature was then slowly raised to 140° and the mixture kept thereat for 2 hr. The mixture was cooled, crushed ice added, and the product extracted with ether. The dark ethereal extracts were shaken with aqueous 2N-sodium hydroxide (3 × 20 ml.), and the alkaline washings acidified. The *chromanone* (1·9 g.) crystallised from ethanol as needles, m. p. 280—282° (Found: C, 70·1; H, 5·8. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%).

2,5,8-*Trimethylchroman-6-ol* (I; $R^1 = R^3 = R^4 = Me$, $R^2 = R^5 = H$).—The chromanone (1·0 g.) in ethanol (100 ml.) was hydrogenated, a palladised charcoal (10%) catalyst being used. The *chromanol* was obtained as white prismatic needles, m. p. 126—128° (from ethanol) (Found: C, 75·0; H, 8·4. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%).

2,5,7,8-*Tetramethylchroman-6-ol* (I; $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = H$).—This chromanol was prepared by hydrogenation of 6-hydroxy-2,5,7,8-tetramethylchroman-4-one [28] and formed white needles from light petroleum (b. p. 40—60°), m. p. 144—146°. John, Günther, and Schmeil [29] give m. p. 145°.

2,2,5,7,8-*Pentamethylchroman-6-ol* (I; $R^1 = R^2 = R^3 = R^4 = R^5 = Me$).—The pentamethyl compound was made according to Smith *et al.*,[12b] m. p. 93—94° (aqueous ethanol) (lit., m. p. 94—94·5°).

2,4,6,7-*Tetramethylcoumaran-5-ol* (II; $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = H$).—This coumaranol was obtained by reduction (hydrogen–palladised charcoal) of 5-hydroxy-2,4,6,7-tetramethylbenzofuran [30] and formed white needles, m. p. 133—134°, from aqueous ethanol. The literature records m. p.s for this compound varying from 123° to 131·5°; cf. Smith *et al.*[12a].

2-*Bromomethylquinol Dimethyl Ether* (V; R = Br).—Toluquinol dimethyl ether (8·0 g.), *N*-bromosuccinimide (9·8 g.), carbon tetrachloride (100 ml.), and benzoyl peroxide (100 mg.) were heated under reflux for 2 hr. After cooling, the mixture was filtered, the solid washed with carbon tetrachloride, and the combined filtrates evaporated. Crystallisation of the solid from light petroleum (b. p. 60—80°) afforded the *bromomethyl derivative* as needles (9·0 g.), m. p. 75—76° (Found: C, 47·2; H, 5·0; Br, 34·1. $C_9H_{11}O_2Br$ requires C, 46·8; H, 4·8; Br, 34·6%). When this was heated with methanol, rapid reaction yielded an oil, b. p. 68°/0·07 mm., n_D^{21} 1·5250, which from the analytical figures appeared to be 2-*methoxymethylquinol dimethyl ether* (Found: C, 65·9; H, 7·6. $C_{10}H_{14}O_3$ requires C, 66·0; H, 7·8%).

1,2-*Bis*-(2,5-*dimethoxyphenyl*)*ethane*.—2-Bromomethylquinol dimethyl ether (8·5 g.) in dry ether (40 ml.) was slowly added to magnesium shavings (0·9 g.) and a crystal of iodine. Reaction proceeded readily and was completed under reflux for 1 hr. The mixture was cooled to room temperature and stirred while a stream of formaldehyde (from 2·2 g. of paraform-formaldehyde) in nitrogen was blown in. After treatment with sulphuric acid (10%; 45 ml.) the ether layer was separated, filtered, and distilled in steam. The residual oil, after isolation with ether, slowly crystallised. The solid (3·3 g.) when crystallised from aqueous ethanol yielded the *diphenylethane*, m. p. 64—66° (Found: C, 71·2; H, 7·4. $C_{18}H_{22}O_4$ requires C, 71·5; H, 7·3%). In subsequent experiments, the oil which separated from the initial reaction was shown to be the diphenylethane; no variation in the experimental conditions was found that would prevent the formation of this product.

5-*Chlorotoluquinol Dimethyl Ether*.—Toluquinol dimethyl ether (9·0 g.), 1,3-dichloro-5,5-dimethylhydantoin [31] (11·8 g.; m. p. 125—132°), benzoyl peroxide (100 mg.), and carbon tetrachloride (80 ml.) were heated under reflux for 30 min. After cooling, the solid was collected, washed with carbon tetrachloride and rejected (9·0 g.; m. p. 120—130°). The combined filtrates were evaporated and the oil taken up in hot light petroleum (30 ml.; b. p. 60—80°). The filtered solution was cooled, large white prisms then separating (5·6 g.), m. p. 86—90°, and a second crop being obtained on concentration of the mother liquors (1·75 g.), m. p. 90—92°. Recrystallisation yielded prisms of 5-*chlorotoluquinol dimethyl ether*, m. p. 92—93° (Found: C, 57·7; H, 5·5; Cl, 19·5. $C_9H_{11}O_2Cl$ requires C, 57·8; H, 5·9; Cl, 19·0%). The product did not give a precipitate with silver nitrate–nitric acid; its infrared absorption corresponded closely with that of 5-bromotoluquinol dimethyl ether.

Chlorination of Toluquinol Dimethyl Ether with Purified 1,3-*Dichloro-5,5-dimethylhydantoin*.—Toluquinol dimethyl ether (9·0 g.), 1,3-dichloro-5,5-dimethylhydantoin (11·8 g., m. p. 131—132°), benzoyl peroxide (50 mg.), and carbon tetrachloride (80 ml.) were heated under reflux for

[28] Werder and Jung, *Ber.*, 1938, **71**, 2650.
[29] John, Günther, and Schmeil, *Ber.*, 1938, **71**, 2637.
[30] Smith and MacMullen, *J. Amer. Chem. Soc.*, 1936, **58**, 629.
[31] B.P. 707,990.

2 hr. The product was obtained in light petroleum, as in the previous experiment, and fractionally crystallised from it, giving as a less-soluble fraction (3·4 g.), 5-chlorotoluquinol dimethyl ether, m. p. 92—93°, and as more-soluble fraction, 2-chloromethylquinol dimethyl ether (2·9 g.), softening at 62—65° and melting at 72° (lit.[20] m. p. 72—73°). Its infrared spectrum differed from that of the nuclear chlorinated product in the longer wavelength region and closely resembled that of 2-bromomethylquinol dimethyl ether. A precipitate was obtained with silver nitrate–nitric acid.

2-*Cyanomethylquinol Dimethyl Ether* (V; R = CN).—Sodium cyanide (5·1 g.) and water (6 ml.) were stirred on the steam-bath while 2-bromomethylquinol dimethyl ether (10·2 g.) in dioxan (100 ml.) was slowly added (30 min.). After a further 5 hr. the mixture was cooled, water added, the product extracted with ether, and the extracts washed with water, dried, and evaporated. Distillation afforded a pale yellow liquid (2·9 g.), b. p. 100—102°/0·05 mm., which solidified, and a viscous yellow oil, b. p. 103—140°/0·05 mm., which was not further investigated. The solid fraction when crystallised from aqueous ethanol furnished the *nitrile* as prisms, m. p. 52—54° (Found: C, 67·3; H, 6·5; N, 7·7. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·3; N, 7·9%).

Homogentisic Acid Dimethyl Ether (V; R = CO_2H).—The nitrile (4·0 g.), sodium hydroxide (1·6 g.), water (2·5 ml.), and ethanol (20 ml.) were heated under reflux for 24 hr. On cooling, the sodium salt separated; water (30 ml.) was added, the ethanol removed under reduced pressure, and the clear solution acidified, a white solid then separating. The acid was collected (4·0 g.); it crystallised from water containing a little ethanol as white needles, m. p. 122—123° (lit.,[20] m. p. 124·5°).

Reduction of Homogentisic Acid Dimethyl Ether.—To a stirred mixture of lithium aluminium hydride (0·6 g.) and dry ether (10 ml.) a solution of the foregoing acid (1·4 g.) in dry ether (50 ml.) was slowly added. The mixture was stirred for 1 hr., cooled, and treated successively with moist ether (15 ml.) and water (10 ml.). The ether layer was separated and dried, the solvent removed, and the residual oil (1·08 g.) distilled in a short-path still to give 2-hydroxyethylquinol dimethyl ether (0·80 g.) [100° (bath)/0·3 mm.], n_D^{23} 1·5378 (Found: C, 65·3; H, 8·0. Calc. for $C_{10}H_{14}O_3$: C, 66·0; H, 7·8%), and an impure higher-boiling fraction (0·13 g.) [110° (bath)/0·3 mm.], the infrared absorption of the ether was identical with that of the product described earlier in this section.

2-2′-*Hydroxyethylquinol Dimethyl Ether* (IV; R = OH).—To magnesium shavings (3·1 g.) were added a few ml. of a solution of 2-bromoquinol dimethyl ether [19] (26·4 g.) in dry ether (100 ml.), and the reaction initiated by the addition of ethyl iodide (1 drop). The remaining ethereal solution was slowly added with stirring so as to maintain reflux, and the reaction completed by heating for 1·5 hr. The solution, after being cooled to 0°, was slowly treated with ethylene oxide (17·0 g.) in dry ether (35 ml.), and the mixture refluxed for 1·5 hr. and decomposed with dilute sulphuric acid (10%). After separation of the ethereal layer the aqueous layer was extracted with ether and the combined ethereal solutions were washed with water and concentrated to a pale yellow oil. Steam-distillation afforded a white solid that crystallised from light petroleum (b. p. 40—60°) as large plates (2·1 g.), m. p. 55° not depressed on admixture with an authentic specimen of quinol dimethyl ether. The oil non-volatile in steam was isolated with ether and distilled, the required *product* being obtained as a pale yellow oil (10·0 g.). On redistillation this had b. p. 108°/0·2 mm., n_D^{25} 1·5370 (Found: C, 65·3; H, 7·9. $C_{10}H_{14}O_3$ requires C, 66·0; H, 7·8%). The 3,5-*dinitrophenylurethane* separated from aqueous acetone as orange-yellow needles, m. p. 166—167° (Found: C, 52·1; H, 4·6; N, 10·8. $C_{17}H_{17}O_8N_3$ requires C, 52·2; H, 4·4; N, 10·7%).

2-2′-*Bromoethylquinol Dimethyl Ether* (IV; R = Br).—A stirred mixture of 2-2′-hydroxyethylquinol dimethyl ether (6·0 g.) in dry ether (30 ml.) containing pyridine (6 drops) was heated under reflux, and phosphorus tribromide (2·3 ml.) in light petroleum (5·0 ml.; b. p. 80—100°) added during 20 min. After a further 1·5 hr. it was cooled and treated with water (10 ml.), the ether layer separated, and the aqueous layer extracted with ether. The combined ethereal extracts were washed successively with saturated aqueous sodium hydrogen carbonate (3 × 15 ml.), N-sodium hydroxide (2 × 10 ml.), and water. Acidification of the sodium hydroxide washings afforded a trace of oil that was rejected. Similar treatment of the sodium hydrogen carbonate solution yielded, after isolation with ether, a yellow oil (2·3 g.), probably the crude dihydrogen phosphite of the starting material, since a clear solution in N-sodium hydroxide (25 ml.), when warmed on the steam-bath for 30 min., precipitated an oil (1·05 g.)

XUM

identified as the unchanged hydroxyethyl derivative. The original ethanol extract was evaporated to give a pale yellow mobile oil (4·15 g.), distillation of which afforded the ***bromoethyl product***, b. p. 93—94°/0·1 mm., n_D^{23} 1·5572 (Found: C, 49·4; H, 5·5; Br, 31·8. $C_{10}H_{13}O_2Br$ requires C, 49·0; H, 5·3; Br, 32·7%). The ***isothiuronium bromide*** separated from acetone as prisms, m. p. 115—116° (Found: C, 41·2; H, 5·5; N, 8·6. $C_{11}H_{17}O_2N_2SBr$ requires C, 41·1; H, 5·3; N, 8·7%). The derived ***picrate*** formed yellow needles, m. p. 215—216°, from ethanol (Found: C, 43·6; H, 3·9; N, 15·1. $C_{17}H_{19}O_9N_5S$ requires C, 43·4; H, 4·1; N, 14·9%).

1-(2,5-*Dimethoxyphenyl*)-3,7,11,15-*tetramethylhexadecan*-3-*ol*.—To magnesium shavings (0·85 g.) and a crystal of iodine were added a few ml. of a solution of 2-2′-bromoethylquinol dimethyl ether (3·98 g.) and ethyl iodide (2·55 g.) in dry ether (20 ml.). Stirring was begun and the remaining solution added at such a rate as to maintain gentle reflux. The mixture was heated for a further 1·5 hr., and then cooled, and a solution of 6,10,14-trimethylpentadecan-2-one (8·7 g.) in dry ether (15 ml.) slowly added. The mixture was then refluxed for 1·5 hr. and cooled, and the complex decomposed by addition of 2N-hydrochloric acid (30 ml.). Ethereal extracts were washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated to give a red oil (11·3 g.). Lower-boiling material was distilled off: (*a*) pale yellow oil (1·07 g.), b. p. 68—70°/0·05 mm., n_D^{19} 1·5026; (*b*) pale yellow oil (3·82 g.), b. p. 114—120°/0·05 mm., n_D^{19} 1·4593, probably crude 3,7,11,15-tetramethylhexadecan-3-ol. The remaining oil was distilled at 5×10^{-3} mm. to give the following fractions: (*a*) pale yellow oil (1·37 g.) [140—150° (bath)], (*b*) yellow oil (0·80 g.) [150—170° (bath)], (*c*) yellow oil (2·67 g.) [170—180° (bath)]. Fraction (*c*) was used for the preparation of tocol and from it the analytical sample of the ***hexadecanol*** was obtained as a yellow oil by a further distillation [170° (bath)/5×10^{-3} mm.], n_D^{20} 1·4788 (Found: C, 78·4; H, 11·6. $C_{28}H_{50}O_3$ requires C, 77·7; H, 11·7%).

Tocol.—The hexadecanol (300 mg.) was heated under reflux with hydrogen bromide in acetic acid (6·0 ml.; 25%) for 8 hr., the dark red solution evaporated, and the residual oil taken up in ether and washed with aqueous sodium hydrogen carbonate and water. The ethereal solution was evaporated and the brown oil (270 mg.; assay 22%) chromatographed in light petroleum (10 ml.; b. p. 40—60°) on alumina (Peter Spence type " O "; 10 × 1 cm.). The chromatogram was developed with benzene–light petroleum (b. p. 40—60°) (150 ml.; 1 : 1); the eluate contained practically no tocol and was rejected, the tocol being recovered by elution with ether (180 ml.). The brown oil (48 mg.) was distilled, affording a yellow oil [160° (bath)/5×10^{-3} mm.] (assay 98%), which on two-dimensional paper-chromatography behaved identically with tocol previously prepared,[22] and had the same infrared spectrum.

Methylation of Tocol.—Tocol (1 g.) was dissolved in a mixture of ethanol (7·8 ml.) and formaldehyde solution (40%; 2·2 ml.), and saturated potassium hydroxide (0·22 ml.) added. The solution was kept at room temperature for 72 hr. Isopropyl ether (free from peroxides; 30 ml.) and concentrated hydrochloric acid (10 ml.) were added and the mixture was heated under reflux for 2 hr. while zinc powder (2 g.) was added in small portions. The ether solution was washed, dried, and evaporated to give a yellow oil.

The oil was chromatographed in light petroleum (b. p. 40—60°) on alumina (Peter Spence, type " O "; 100 g.). The column was rendered fluorescent before use as follows: alumina (5 g.) was mixed with a 0·1% solution of sodium fluorescein in methanol (25 ml.), filtered off, and washed with methanol. It was dried at 200° for 1 hr. and then intimately mixed with the remaining 95 g. of alumina. The column was developed with benzene, then benzene containing 1% v/v of ethanol. The column was extracted under ultraviolet light, and the dark tocopherol band cut out and extracted with ethanol. Evaporation gave a yellow oil (300 mg.; 97% purity by analysis) which was distilled [170° (bath)/5×10^{-3} mm.] to give 5-methyltocol, identical with that prepared by McHale *et al.*[1] (paper chromatography, ultraviolet absorption, and infrared spectrum) (Found: C, 80·1; H, 11·5. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·5%).

Oxidation of (±)-α-*Tocopherol*.—(±)-α-Tocopherol (1·2 g.) was oxidised by Fernholz's method.[24] Distillation [140° (bath)/5×10^{-3} mm.] of the neutral fraction (0·56 g.) gave 4-hydroxy-4,8,12,16-tetramethylheptadecanoic lactone, n_D^{21} 1·4600, identical in refractive index and infrared spectrum with the lactone obtained from (+)-α-tocopherol. The *S*-benzylisothiuronium salts prepared from both lactones had m. p. and mixed m. p. 117—118°.

Oxidation of Tocol.—Tocol (3 g.) was oxidised in the same manner. Distillation [140° (bath)/5×10^{-3} mm.] of the neutral fraction (1 g.) gave a lactone, n_D^{20} 1·4590, from which an *S*-benzylisothiuronium salt, m. p. 117—118°, was prepared. The lactone had the same infrared spectrum as 4-hydroxy-4,8,12,16-tetramethylheptadecanoic lactone.

Chloromethylations.—(*a*) Synthetic 5-methyltocol (80 mg.) and paraformaldehyde (50 mg.) were dissolved in dry ether saturated with hydrogen chloride (5 ml.), and kept for 2 hr. More ether and concentrated hydrochloric acid (5 ml.) were added, followed by an excess of zinc dust (*ca.* 0·5 g.) added during 30 min. The ethereal solution was separated, washed twice with water, and evaporated to give a pale yellow oil (71 mg.) containing 28·5% of β-tocopherol and 26·4% of α-tocopherol, identified by two-dimensional paper-chromatography. The product (2 mg.) was chromatographed on paper impregnated with zinc carbonate, and the β-tocopherol band removed (*ca.* 500 μg.) and separately nitrosated. The nitroso-derivative behaved identically, on two-dimensional chromatography, with authentic 7-nitroso-β-tocopherol. The remainder of the product was chloromethylated for a further 3 hr. The product (65 mg.) then contained 53·5% of α-tocopherol and no β-tocopherol. It was chromatographed on a column (2·5 cm. × 20 cm.) of zinc carbonate–Hyflo Super-cel (1 : 1; rendered fluorescent by mixing the column packing with a 0·02% w/v solution of sodium fluorescein in methanol, washing it with methanol, and then drying it at 150° for 1 hr.) in light petroleum (60—80°), and the column developed with benzene–light petroleum (1 : 2). The column was extracted under ultraviolet light, and the dark band due to the tocopherol cut out and eluted with ether. Evaporation and distillation [160° (bath)/5 × 10^{-3} mm.] gave α-tocopherol (infrared spectrum identical with that of an authentic sample).

(*b*) 8-Methyltocol (20 mg.) and paraformaldehyde (50 mg.) were dissolved in dry ether saturated with hydrogen chloride (5 ml.) and kept for 5 min. Reduction with zinc dust and hydrochloric acid and working up gave a product containing 22% of β-tocopherol, 27·7% of an unknown reducing substance, and some starting material. In another reaction, after 30 min. the product contained 47·6% of β-tocopherol. No 7,8-dimethyltocol could be detected (*o*-dianisidine coupling test).

(*c*) 7-Methyltocol (1 mg.) and paraformaldehyde (0·4 mg.) were dissolved in dry ether saturated with hydrogen chloride (5 ml.) and kept for 30 min. After reduction and working up, the product contained 34% of 5,7-dimethyltocol and 48% of unchanged 7-methyltocol.

(*d*) 5,7-Dimethyltocol (1 mg.) was treated as in (*c*) above; the product contained 36% of α-tocopherol.

(*e*) ε-Tocopherol (1 mg.) was treated as in (*c*) above. The product contained 18% of a substance, chromatographically identical with a specimen of natural ζ-tocopherol from wheat bran (R_F = 0·36). Continuing the reaction for 4 hr. did not produce α-tocopherol.

Hydroxymethylations.—(*a*) 5-Methyltocol (1 mg.) was dissolved in a mixture of ethanol (0·75 ml.) and formaldehyde solution (40%; 0·2 ml.), and saturated potassium hydroxide solution (0·02 ml.) was added. After 3 days, isopropyl ether (10 ml.), concentrated hydrochloric acid (5 ml.), and zinc dust (0·5 g.) were added, and the mixture was heated under reflux at 60° for 2 hr. The ethereal solution was separated, washed three times with water, and evaporated to give a product which contained no identifiable products.

(*b*) ε-Tocopherol (1 mg.) was treated as in (*a*) above. The product, on chromatographic separation, contained 21% of a substance identical with ζ-tocopherol from wheat bran (R_F = 0·36).

(*c*) 7-Methyltocol (50 mg.) was dissolved in a mixture of ethanol (3 ml.), formaldehyde solution (40%; 0·3 ml.), and potassium hydroxide (0·1 g.). The solution was heated in a sealed ampoule at 65° for 1 hr. After reduction and working up the product contained 7·8% of 5,7-dimethyltocol (R_F = 0·28, identical with that of an authentic specimen), and 81% of unchanged material.

(*d*) 8-Methyltocol (50 mg.) was treated as in (*c*) above for 30 min. After reduction and working up, the product contained 47·4% of 5,8-dimethyltocol and 40% of unchanged material.

Chromatography of 5,7-Dimethyltocol and ζ-Tocopherols.—Specimens of ζ-tocopherol were obtained from wheat bran, palm oil, and unpolished rice as previously described.[5,26] These substances (20 μg.), together with 20 μg. of synthetic 5,7-dimethyltocol, were run side by side for 4 hr. by the descending method, Whatman No. 4 papers being used. The ζ-tocopherol from wheat bran and palm oil had an R_F value of 0·36. The ζ-tocopherol from rice and 5,7-dimethyltocol had an R_F value of 0·28.

The authors thank Miss J. Mallion and Mr. M. Rix for their assistance.

WALTON OAKS EXPERIMENTAL STATION,
VITAMINS LTD., TADWORTH, SURREY.

[*Received, March 2nd,* 1959.]

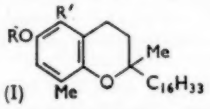
XUM

681. *Tocopherols. Part VI.* A Novel Synthesis of 8-Methyltocol.*

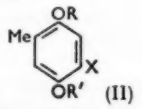
By J. Green, D. McHale, P. Mamalis, and S. Marcinkiewicz.

Racemic 8-methyltocol has been synthesised by two routes, one of which also gives 7-methyltocol.

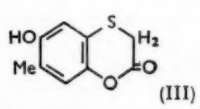
8-Methyltocol (δ-tocopherol) (I; R = R′ = H), isolated from soybean oil by Stern, Robeson, Weisler, and Baxter,[1] had similar properties to a monomethyltocol previously prepared from phytol and toluquinol 4-benzoate (II; R = X = H, R′ = Bz) by Jacob, Sutcliffe, and Todd.[2] Mamalis, Green, Marcinkiewicz, and McHale[3] observed that the toluquinol 4-benzoate was contaminated with the 1-benzoate (II; R′ = X = H, R = Bz) and that this probably accounted for the report[4] that 7-methyltocol was a product of the condensation of phytol with the 4-benzoate. The presence of 7-methyltocol in the synthetic 8-methyltocol would also explain the variation[1] in the melting point of the 2,6-dimethylquinols derived by pyrolysis from synthetic 8-methyltocol and from natural 8-methyltocol. The 7-methyltocol would yield 2,5-dimethylquinol which would not have separated readily from 2,6-dimethylquinol. Although the use of pure toluquinol 4-benzoate gave 8-methyltocol free from isomers, the yield was poor and the purification difficult. An alternative synthesis was therefore sought.



(I)



(II)



(III)

Because of the difficulty of separating isomeric mixtures of the monomethyltocols, neither the condensation[5] of toluquinol with phytol to give a mixture of 5-, 7-, and 8-methyltocol, nor the condensation[6] of 5-methylthiotoluquinol (II; R = R′ = H, X = SMe) with phytol, which gave a mixture of 5- and 8-methyltocol, afforded a satisfactory route to pure 8-methyltocol. Since the condensation of pure toluquinol 4-benzoate with phytol gave 8-methyltocol, free from isomers, it was thought that esterification of the 4-hydroxyl group of a 5-alkylthiotoluquinol (II; R = R′ = H, X = SAlk) might prevent formation of 5-methyltocol during the condensation with phytol. 5-Bromotoluquinol (II; R = R′ = H, X = Br)[7] was readily converted into 5-mercaptotoluquinol (II; R = R′ = H, X = SH) by refluxing alcoholic sodium sulphide. This method was superior to that used by Karrer and Dutta.[6] Treatment of the thio-compound with chloroacetic acid gave 5-carboxymethylthiotoluquinol (II; R = R′ = H, X = S·CH_2·CO_2H), which was cyclised to the benzo-1,4-oxathiinone (III) at 180°. Condensation of this compound with phytol, subsequent desulphurisation with Raney nickel, and hydrolysis gave a product containing 20% of 8-methyltocol. Chromatography followed by molecular distillation gave pure 8-methyltocol, with infrared spectrum identical with that of natural δ-tocopherol. Stern *et al.*[1] found that the *p*-phenylazobenzoate of natural δ-tocopherol was a low-melting solid; in view of its racemic nature it was not surprising, therefore, that the *p*-phenylazobenzoate of synthetic 8-methyltocol was an oil at ordinary temperatures.

Because it was thought that the low yields obtained in the preparation of 8-methyltocol from toluquinol 4-benzoate were due to the deactivating influence on the ring of the benzoyloxy-group, the condensation of toluquinol 4-methyl ether (II; R = X = H, R′ = Me) with phytol was examined, the necessary ether being obtained together with

* Part V, preceding paper.

[1] Stern, Robeson, Weisler, and Baxter, *J. Amer. Chem. Soc.*, 1947, **69**, 869.
[2] Jacob, Sutcliffe, and Todd, *J.*, 1940, 327.
[3] Mamalis, Green, Marcinkiewicz, and McHale, *J.*, 1959, 3350.
[4] Pendse and Karrer, *Helv. Chim. Acta*, 1958, **41**, 396.
[5] Marcinkiewicz, McHale, Mamalis, and Green, following paper.
[6] Karrer and Dutta, *Helv. Chim. Acta*, 1948, **31**, 2080.
[7] McHale, Mamalis, Green, and Marcinkiewicz, *J.*, 1958, 1600.

toluquinol dimethyl ether (II; R = R′ = Me, X = H) by the partial methylation of toluquinol. Contrary to expectation, the demethylated product from the condensation of toluquinol 4-methyl ether and phytol consisted of two parts of 7- and one part of 8-methyltocol; and, because the 4-hydroxyl group was blocked by a methyl group, the 7-methyltocol must have been present, before demethylation, as the open-chain 4-methoxy-phenol (II; R = H, R′ = Me, X = CH_2·CH:CMe·$C_{16}H_{33}$), and the 8-methyltocol as a methyl ether (I; R = Me, R′ = H). These two compounds were separated by selective adsorption on alumina, and purified by distillation, and demethylated to 7- and 8-methyltocol.

The high-boiling residue from the distillation of 8-methyltocol methyl ether, on molecular distillation, gave a viscous oil that gave correct analytical results for a phytyl-substituted 8-methyltocol methyl ether, probably of structure (I; R = Me, R′ = CH_2·CH:CMe·$C_{16}H_{33}$).

Experimental

All tocopherol assays were carried out as described by Green, Marcinkiewicz, and Watt.[8]

5-Mercaptotoluquinol (II; R = R′ = H, X = SH).—5-Bromotoluquinol [7] (20 g.) and sodium sulphide (30 g.) in 95% ethanol were refluxed for 2 hr. and then acidified (concentrated hydrochloric acid) at the b. p. The mixture was cooled and diluted with ether, and the ethereal solution washed several times with water, dried, and evaporated. The solid obtained was dried *in vacuo* over calcium chloride. Crystallisation from water gave 5-thiotoluquinol (10·8 g.), m. p. 186—188° (Found: C, 53·6; H, 4·8; S, 20·4. Calc. for $C_7H_8O_2S$: C, 53·8; H, 5·2; S, 20·5%).

5-Carboxymethylthiotoluquinol (II; R = R′ = H, X = S·CH_2·CO_2H).—5-Mercaptotoluquinol (7·3 g.) and chloroacetic acid (4·7 g.) in ether were shaken for 2 hr. with a solution of sodium carbonate (5·2 g.) in water (50 ml.) containing sodium dithionite (1 crystal). The aqueous layer was separated, acidified with concentrated hydrochloric acid, and extracted with ether. The extract was dried and evaporated to give *5-carboxymethylthiotoluquinol* (8·2 g.), m. p. 168—170° [from ethyl acetate–light petroleum (b. p. 40—60°)] (Found: C, 50·4; H, 4·6; S, 15·1. $C_9H_{10}O_4S$ requires C, 50·5; H, 4·7; S, 15·0%).

2,3-Dihydro-6-hydroxy-7-methylbenzo-1,4-oxathiin-2-one (III).—5-Carboxymethylthiotoluquinol (0·8 g.) was heated at 180° for 1 hr. Crystallisation of the product from benzene gave the *benzoxathiinone* (0·6 g.), m. p. 163—164° (Found: C, 55·0; H, 3·9; S, 16·2. $C_9H_8O_3S$ requires C, 55·1; H, 4·1; S, 16·3%).

8-Methyltocol (I; R = R′ = H).—The benzoxathiinone (5·0 g.), phytol (7·5 g.), benzene (50 ml.), and anhydrous formic acid (50 ml.) were heated under reflux for 14 hr. The benzene layer was separated, washed with N-sodium hydroxide and water, and concentrated to an oil (7·3 g.) which was taken up in ethanol (200 ml.) and refluxed for 8 hr. with Raney nickel (7 g.). After the mixture had cooled, it was filtered through Hyflo Super-cel. The filtrate was heated to the boil and potassium hydroxide (2·5 g.) added through the condenser. After 20 min. concentrated hydrochloric acid (5 ml.) was added to the refluxing solution. The organic layer was diluted with light petroleum (b. p. 40—60°), washed with water and saturated aqueous sodium hydrogen carbonate, and concentrated to an oil (5·9 g.) which contained 22% of 8-methyltocol. This concentrate was adsorbed from light petroleum (b. p. 40—60°) on alumina (Peter Spence type " O "; 50 g.). After elution of the impurities with light petroleum, followed by benzene, the tocol was eluted with ether. Evaporation gave a pale brown oil (0·9 g.) which contained 91% of 8-methyltocol (by assay). Molecular distillation [150° (bath)/10^{-3} mm.] gave pure 8-methyltocol, $\nu_{max.}$ 3360 m, 2915 vs, 1605 w, 1460 vs, 1375 s, 1340 m, 1295 m, 1210 s, 1145 m, 1100 w, 1040 w, 990 m, 938 m, 855 m, 795 w, 717 m cm.$^{-1}$ (liquid film).

8-Methyltocol p-Phenylazobenzoate.—8-Methyltocol (91% concentrate; 0·15 g.) in dry ethylene dichloride (5 ml.) containing pyridine (1 ml.) was treated with *p*-phenylazobenzoyl chloride (0·15 g.) in dry ethylene dichloride (5 ml.) and refluxed for 1 hr. Water (5 ml.) was added, after 1 hr. the product was taken up in light petroleum (b. p. 40—60°), and the solution washed with dilute hydrochloric acid and then with water. The organic layer was filtered and concentrated, the oil was redissolved in light petroleum, and the solution filtered and concentrated. The red oil (0·2 g.) on distillation [250° (bath)/10^{-3} mm.] gave the *p-phenylazobenzoate* (Found: C, 78·3; H, 9·0; N, 4·8. $C_{40}H_{54}O_3N_2$ requires C, 78·7; H, 8·8; N, 4·6%).

[8] Green, Marcinkiewicz, and Watt, *J. Sci. Food Agric.*, 1955, **6**, 274.

Toluquinol 4-Methyl Ether (II; R = X = H, R′ = Me).—Methyl iodide (20 ml.) was added rapidly to a stirred mixture of toluquinol (12·4 g.), anhydrous potassium carbonate (13·8 g.), and acetone (30 ml.), and the whole refluxed for 4 hr. Steam-distillation gave an oil (6·7 g.) which was taken up in ether and extracted into N-sodium hydroxide. The alkaline extract was acidified and extracted with ether. Evaporation of the dried extract gave toluquinol 4-methyl ether (3·3 g.), m. p. 72°, from ether–light petroleum (b. p. 40—60°) (Bamberger [9] gave m. p. 70·5—71·5°). The dried alkali-insoluble extract on evaporation gave toluquinol dimethyl ether (2·3 g.), n_D^{19} 1·5210.

Condensation of Toluquinol 4-Methyl Ether with Phytol.—Toluquinol 4-methyl ether (7 g.), phytol (15 g.), dry benzene (75 ml.), and anhydrous formic acid (75 ml.) were heated under reflux for 6 hr. The benzene layer was separated, washed with N-sodium hydroxide and water, and concentrated to a straw-coloured oil (19·5 g.). A sample (1·0 g.) was refluxed for 3 hr. with hydrobromic acid (5 g.) in acetic acid (15 ml.), then diluted with light petroleum (b. p. 40—60°) and washed successively with water, saturated aqueous sodium hydrogen carbonate, dilute hydrochloric acid, and water. Evaporation gave a pale brown oil which contained 22% of 7-methyltocol and 13·6% of 8-methyltocol.

The remainder of the original oil was taken up in light petroleum (b. p. 40—60°; 50 ml.) and adsorbed on alumina (Peter Spence type " O "; 120 g.). Elution gave the following fractions: (1), 5·0 g., n_D^{19} 1·4887, (2) 5·8 g., n_D^{20} 1·4880, both eluted by light petroleum; (3), 4·2 g., n_D^{20} 1·5028, eluted by benzene; (4), 1·3 g., n_D^{18} 1·4865; and (5), 0·4 g., n_D^{24} 1·5150 both eluted by ether. Distillation of fraction (1) gave three fractions: (1a), 1·0 g., b. p. 120—130°/0·1 mm., n_D^{18} 1·4761; (1b), 0·7 g., b. p. 130—180°/0·1 mm., n_D^{20} 1·4869; and (1c), 2·5 g., b. p. 200—210°/0·1 mm. Fraction (1c) was refluxed for 3 hr. with hydrobromic acid (7·5 g.) in acetic acid (20 ml.), and the product, worked up as above, gave a pale brown oil (2·5 g.) which contained 32% of 8-methyltocol. Further purification was carried out by adsorption from light petroleum (b. p. 40—60°) on alumina (Peter Spence type " O "; 50 g.). After development with light petroleum followed by benzene, the tocol was eluted with ether. Evaporation gave a pale brown oil (0·8 g.), which after distillation [150° (bath)/10^{-3} mm.] gave pure 8-methyltocol as a pale yellow viscous oil.

Fraction (2) on distillation gave three fractions: (2a) a yellow mobile oil (1·0 g.), b. p. 150—180°/0·1 mm., n_D^{19} 1·4729; (2b) a viscous yellow oil (1·9 g.), b. p. 210°/0·1 mm., n_D^{19} 1·4955; (2c) a viscous yellow oil (1·4 g.), b. p. 220°/0·1 mm., n_D^{19} 1·5000. Fraction (2b) was refluxed for 3 hr. with hydrobromic acid (5 g.) in acetic acid (15 ml.), and the product worked up in the usual way to give a pale brown oil (1·7 g.), which contained 14·5% of 7-methyltocol and 25% of 8-methyltocol.

Fraction (2c) was dissolved in ethanol (20 ml.) and shaken with hydrogen and palladised charcoal till hydrogen uptake ceased. After filtration and evaporation the resulting oil was refluxed for 3 hr. with hydrobromic acid (5 g.) and acetic acid (15 ml.), and the product isolated in the usual way. Paper-chromatographic assay showed that the product contained 12·5% of 8-methyltocol and some reducing material which remained on the origin-line and was presumably the quinol derived from the reduced methoxy-phenol (II; R = H, R′ = Me, X = $[CH_2]_2$·CHMe·$C_{16}H_{33}$).

The residues from the distillation of fractions (1) and (2) were combined and distilled [220° (bath)/10^{-3} mm.], giving a pale yellow, viscous oil which was presumably *8-methyl-5-phytyltocol methyl ether* (I; R = Me, R′ = CH_2·CH:CMe·$C_{16}H_{33}$) (Found: C, 83·0; H, 12·5. $C_{45}H_{86}O_2$ requires C, 82·9; H, 12·4%).

Fraction 3 distilled as a yellow mobile oil (3·8 g.), b. p. 220°/0·1 mm. Distillation [190° (bath)/10^{-3} mm.] gave pure *5-phytyltoluquinol 4-methyl ether* (II; R = H, R′ = Me, X = CH_2·CH:CMe·$C_{16}H_{33}$), n_D^{19} 1·5030 (Found: C, 80·6; H, 11·2. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%). This compound (3·6 g.) was refluxed for 8 hr. with hydrobromic acid (15 g.) in acetic acid (45 ml.) and, on isolation in the usual way, gave a red oil (3·5 g.) which contained 78% of 7-methyltocol and could not be further purified by molecular distillation.

The authors are grateful to Mr. P. R. Watt for the infrared spectra and to Mr. D. J. Outred for technical assistance.

WALTON OAKS EXPERIMENTAL STATION, VITAMINS, LTD.,
TADWORTH, SURREY.

[*Received, March 2nd,* 1959.]

[9] Bamberger, *Annalen*, 1912, **390**, 174.

682. *Tocopherols. Part VII.* The Condensation of Toluquinol with Phytol.*

By S. Marcinkiewicz, D. McHale, P. Mamalis, and J. Green.

The condensation of toluquinol with phytol leads to a 1 : 2 : 1 mixture of 5-, 7-, and 8-methyltocol.

A recent paper by Pendse and Karrer [1] on the nature of the products of condensation of toluquinol and phytol, a reaction first examined by Karrer and Fritzsche,[2] prompts us to record our observations on this reaction.

When examined by the paper-chromatographic technique [3] and by the differential nitroso-assay,[4] the initial product proved to be a 71% concentrate containing 5-, 7-, and 8-methyltocol in an approximate ratio of 1 : 2 : 1. An attempt to prepare a *p*-nitrophenylurethane from this concentrate gave only a gum.

It was possible to separate the 8-methyltocol from the 5- and 7-methyltocol by chromatography. The two fractions obtained were further purified by molecular distillation, pure 8-methyltocol and a concentrate containing 32% of 5-methyltocol and 56% of 7-methyltocol being obtained. This concentrate gave a *p*-nitrophenylurethane, m. p. 109—111°, which did not depress the m. p. of the *p*-nitrophenylurethane, m. p. 112°, prepared from an authentic specimen of 7-methyltocol.[5] Pendse and Karrer reported m. p. 86—87° for a *p*-nitrophenylurethane prepared from their purified 7-methyltocol. The difference in m. p. between authentic 7-methyltocol *p*-nitrophenylurethane and Pendse and Karrer's derivative indicates that the latter's 7-methyltocol was not pure and was probably contaminated with 5- and 8-methyltocol.

Experimental

Condensation of Toluquinol with Phytol.—Toluquinol (6·2 g.), phytol (14 g.), dry benzene (50 ml.), and anhydrous formic acid (50 ml.) were heated under reflux for 4 hr. The benzene layer was separated, washed with N-sodium hydroxide and water, and concentrated to a straw-coloured oil (18·6 g.) which contained 8-methyltocol (21%), 5-methyltocol (18%), and 7-methyltocol (32%). A portion (3 g.) of this oil was adsorbed from light petroleum (b. p. 40—60°) on to alumina (Peter Spence type " H "; 100 g.), which contained a small quantity of alumina previously treated with sodium fluorescein in methanol and activated at 150° for 1 hr. After development with light petroleum, the dense mixed methyltocol band, which could be detected by the quenching of the fluorescence under ultraviolet light, was cut from the column, extracted with ether–ethanol (3 : 1) and combined with the extract of a second portion of oil similarly treated. The combined extract was rechromatographed on alumina (100 g.) and, after development with light petroleum, gave two bands which were extracted separately from the column with ether–ethanol. Evaporation of the extract of the leading band gave an oil (1·48 g.), which contained 56% of 5- and 7-methyltocol. Since the extract of the following band when run on paper treated with zinc carbonate [3] gave two bands, this material was rechromatographed on alumina and the front portion of the band discarded. Extraction, after cutting the column, gave an oil containing 71% of 8-methyltocol. Distillation at 150° (bath)/10^{-3} mm. gave pure 8-methyltocol (130 mg.).

Distillation [150° (bath)/10^{-3} mm.] of the mixture of 5- and 7-methyltocol gave an 88% concentrate containing 32% of 5-methyltocol and 56% of 7-methyltocol.

p-*Nitrobenzazide.*—A stirred solution of *p*-nitrobenzoyl chloride (10 g.) in acetic acid (30 ml.) was treated with sodium azide (3·5 g.), and the precipitated solid collected. Dilution of the filtrate with water gave *p*-nitrobenzazide (7·1 g.), m. p. 71—74° (after drying *in vacuo* over

* Part VI, preceding paper.

[1] Pendse and Karrer, *Helv. Chim. Acta*, 1958, **41**, 396.
[2] Karrer and Fritzsche, *ibid.*, 1939, **22**, 260.
[3] Green, Marcinkiewicz, and Watt, *J. Sci. Food Agric.*, 1955, **6**, 274.
[4] Marcinkiewicz and Green, *Analyst*, 1959, **84**, 304.
[5] McHale, Mamalis, Green, and Marcinkiewicz, *J.*, 1958, 1600.

XUM

calcium chloride). Though not pure (Sah and Chiao [6] gave m. p. 77—78°) this material was suitable for the preparation of nitrophenylurethanes.

p-*Nitrophenylurethane from the Concentrate of* 5- *and* 7-*Methyltocol.*—88% Concentrate (0·3 g.), *p*-nitrobenzazide (0·6 g.), and toluene (10 ml.) were refluxed for 2 hr. The solid was filtered off and washed with benzene. The filtrate and benzene washings were combined and evaporated, and the product hydrolysed by aqueous acetone for 1 hr. The mixture was diluted with benzene, washed free from acetone, filtered, and concentrated. Crystallisation of the oil from methanol gave a solid (50 mg.), m. p. 109—111°, which was not depressed on admixture with authentic 7-methyltocol *p*-nitrophenylurethane.

7-*Methyltocol* p-*Nitrophenylurethane.*—7-Methyltocol [5] (0·3 g.) when treated as above gave 7-*methyltocol* p-*nitrophenylurethane* (0·15 g.), m. p. 112° (from methanol) (Found: C, 72·3; H, 8·5; N, 4·7. $C_{34}H_{50}O_5N_2$ requires C, 72·1; H, 8·9; N, 4·9%).

WALTON OAKS EXPERIMENTAL STATION, VITAMINS, LTD.,
TADWORTH, SURREY. [*Received, March 2nd,* 1959.]

[6] Sah and Chiao, *Rec. Trav. chim.*, 1939, **58**, 595.

---

683. *Diaryls. Part II.*[1] *The Rearrangement of* 1,2′-*Hydrazonaphthalene.*

By E. R. WARD and B. D. PEARSON.

1,2′-Hydrazonaphthalene rearranges in acid media to give 1′,2-diamino-1,2′-binaphthyl. This result is compared with the analogous rearrangement of the two isomeric hydrazonaphthalenes, and a general mechanism involving a π-complex transition state is formulated.

Ultraviolet spectra of four dinitrobinaphthyls are interpreted in relation to the possible steric effects within such molecules.

Pyrolyses of 1,2′-binaphthyl-1′,2-iodonium iodide failed to yield 1,2:5,6-dibenzobiphenylene.

A new preparation of 2-nitro-1-naphthylamine from naphthionic acid is described.

AFTER reaction of ethereal 1-bromo-2-iodonaphthalene with magnesium Ward and Pearson [1] were able to isolate, in minute yield, a hydrocarbon which may have been 1,2:5,6-dibenzobiphenylene. We have now attempted to prepare this from 1,2′-binaphthyl-1′,2-iodonium iodide, but pyrolyses of the latter under varying conditions (cf. Ward and Pearson,[1] Curtis and Viswanath [2]) failed.

The iodonium iodide was obtained from 1′,2-diamino-1,2′-binaphthyl. This compound was prepared by Cook *et al.*[3] by reduction of 1,2′-azonaphthalene to 1,2′-hydrazonaphthalene and subsequent rearrangement, but they did not orientate it. We have now established its constitution by obtaining it by catalytic reduction of 1′,2-dinitro-1,2′-dinaphthyl, the latter being isolated in 40% yield from a crossed Ullmann reaction between 2-iodo-1- and 1-iodo-2-nitronaphthalene (which also produced a small amount of 1,1′-dinitro-2,2′-dinaphthyl but apparently no 2,2′-dinitro-1,1′-dinaphthyl). This new route is rendered impracticable by the difficulty in preparing 2-nitro-1-naphthylamine on a large scale. An attractive route to the nitro-amine appeared to be nitration of *N*-acetylnaphthionic acid (the sulphonic acid group acting as a blocking group), followed by hydrolysis and desulphonation of the 4-acetamido-3-nitronaphthalene-1-sulphonic acid. Although the last stages can be satisfactorily performed in a combined process the nitration gives erratic results.

Cook *et al.* prepared 1,2′-azonaphthalene by deamination of the product obtained by coupling diazotised 2-naphthylamine with 1-naphthylamine hydrochloride in water. This deamination was originally carried out by Nietzki and Gottig [4] and has been repeated by

[1] The Paper by Ward and Pearson, *J.*, 1959, 1676, is regarded as Part I.
[2] Custis and Viswanath, *J.*, 1959, 1670.
[3] Cook, Hewett, and Kennaway, *Amer. J. Cancer*, 1940, **40**, 62.
[4] Nietzki and Gottig, *Ber.*, 1887, **20**, 612.

Badger and Lewis.[5] Since none of these workers separated the 4-amino-1,2′-azonaphthalene before its deamination it appeared to us that the reported differences in m. p. of the deamination product might be due to the presence, in varying amount, of the isomeric 2,2′-azonaphthalene. However the product we obtained by deaminating the mixed azocompounds proved identical with that obtained by deaminating pure 4-amino-1,2′-azonaphthalene (separated from the coupling product by chromatography on alumina [6]). This confirms Turner's suggestion [7] that in the diazotisation and deamination of the mixed aminoazo-compounds arising from coupling a diazo-compound with 1-naphthylamine the 1-amino-2-azonaphthalenes are converted into naphthotriazoles in the diazotisation and subsequently eliminated in working up the product. Attempts to prepare 1,2′-azonaphthalene by desulphonation of 1′,2-azonaphthalene-5-sulphonic acid (Acilan Braun 4G,C.I. 13,000), with 50% or 70% aqueous sulphuric acid, were not successful.

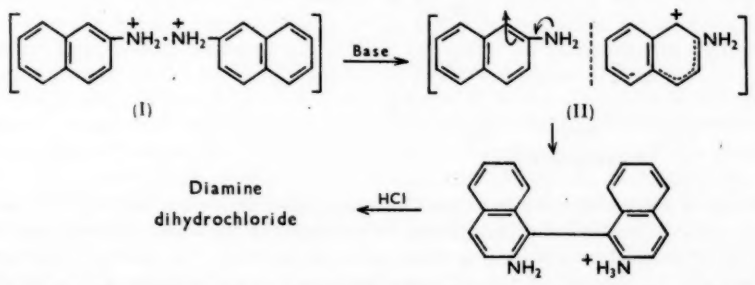
The yield of 1′,2-diamino-1,2′-dinaphthyl was improved from the 20% claimed by Cook *et al.*, who used sodium dithionite as reducing agent, to 95% by using zinc powder and ammonia (cf. Vecera, Petranek, and Gasparic [8]). Paper chromatography showed that the crude rearrangement product from 1,2′-hydrazonaphthalene contained no component in addition to the identified 1′,2-diamino-1,2′-dinaphthyl.

For the first time the rearrangements of the three hydrazonaphthalenes can be studied qualitatively. The results are summarised in Table 1. The results are similar to the electrophilic substitution of naphthalene derivatives containing an electron-releasing group (*e.g.*, NH_2). The most reactive positions in 1-naphthylamine derivatives are the 2- and the 4-position, and in 2-naphthylamine derivatives the 1-position. One scheme for formulating intramolecular attack by an electrophilic entity on an electron-releasing entity by using the doubly protonated transition state (I) identified by Hammond and

TABLE 1.

Hydrazonaphthalene	Product
2,2′-	1,1′-Diamino-2,2′-binaphthyl [9, 10]
1,2′-	1′,2-Diamino-1,2′-binaphthyl
1,1′-	2,2′- and 4,4′-Diamino-1,1′-binaphthyl (about equal amounts) [11]

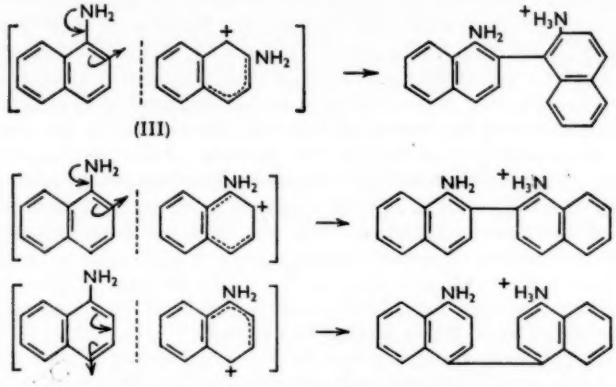
Shine [12] is as annexed. Hughes and Ingold [13] pointed out that the transition state (I) offers an exceptional amount of extra resonance energy and owing to the proximity of the two



planar naphthalene molecules a π-complex, as proposed by Dewar,[14] may be favoured. Removal of a proton from the transition state, accomplished by a suitable base (cf.

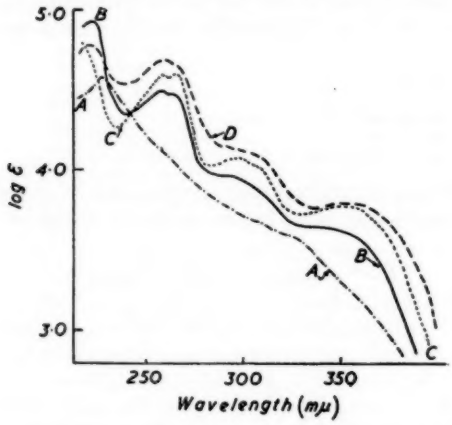
[5] Badger and Lewis, *J.*, 1953, 2154.
[6] Ward, Wells, and Pearson, *J. Soc. Dyers and Colourists*, in the press.
[7] Turner, *J.*, 1949, 2282.
[8] Vecera, Petranek, and Gasparic, *Chem. Listy*, 1957, **51**, 911.
[9] Meisenheimer and Witte, *Ber.*, 1903, **36**, 4159.
[10] Cumming and Howie, *J.*, 1932, 528.
[11] Hodgson and Habeshaw, *J.*, 1947, 77.
[12] Hammond and Shine, *J. Amer. Chem. Soc.*, 1950, **72**, 220.
[13] Hughes and Ingold, *J.*, 1941, 608.
[14] Dewar, "Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949, p. 236.

Dewar [14]), would then lead to a second π-complex (II) in which an intramolecular carbonium-ion attack takes place on the adjacent naphthalene nucleus. This attack forms the diaminobinaphthyl and liberates a second proton for salt formation. That carbonium



(III)

ion will be formed which has the greatest stabilisation energy. The positions of highest electron-density on the other naphthalene nucleus will be adjacent to the positively charged atom (provided the polarisibility and localisation energy of the carbon atoms are suitable).



Ultraviolet spectra of (*A*) **1,1′-dinitro-2,2′-**, (*B*) **1′,2-dinitro-1,2′-**, (*C*) **2,2′-dinitro-1,1′-**, *and* (*D*) **3,3′-dinitro-2,2′-binaphthyl** *in ethanol.*

Whereas in the benzene series within the π-complex relative nuclear rotation can occur (leading to the formation of diphenylines) in the naphthalene series this rotation may be prevented by an electrostatic locking effect initiated by the second nucleus (due to charge transference). In the case of the unsymmetrical hydrazonaphthalene it is assumed that the carbonium ion (III) predominates, the steric arrangement then causing formation of the 1,2′-bond, formation of the 1,4′-bond being impossible without molecular rotation within the complex (III).

The ultraviolet spectra of the four dinitrobinaphthyls (Table 2) can be interpreted in terms of steric hindrance to conjugation within the binaphthyl molecule. Friedel, Orchin, and Reggel [15] deduced from the spectra of the binaphthyls that although there was steric hindrance to conjugation in 1,1′-binaphthyl, and to a small extent in 1,2′-dinaphthyl, 2,2′-binaphthyl was comparatively free from steric hindrance and hence planar.

[15] Friedel, Orchin, and Reggel, *J. Amer. Chem. Soc.*, **1948**, **70**, 199.

The spectrum of 1,1′-dinitro-2,2′-binaphthyl, as is usual for a large conjugated molecule, has little fine structure; only the band at 228 mμ can be identified with a bathochromic shift of the band at 212 mμ in the spectrum of 2,2′-dinaphthyl.

The spectra of 2,2′-dinitro-1,1′- and 3,3′-dinitro-2,2′-binaphthyl are very similar to the spectrum of 2-nitronaphthalene, indicating that there is little conjugation between the naphthalene nuclei in these two binaphthyls. 1′,2-Dinitro-1,2′-binaphthyl also possesses a spectrum quite like that of 2-nitronaphthalene, but there is some smoothing out of the fine structure, which suggests that a small measure of conjugation is present.

TABLE 2. *Ultraviolet spectral maxima* (log ε *in parentheses*) *for ethanol solution.*

Dinitrobinaphthyl					
1,1′-NO_2	-2,2′- (*A*)	228(4·59)			
1′,2-	-1,2′- (*B*)	222(4·92)	258(4·46) 264(4·44)	293(3·95) †	350(3·6) †
2,2′-	-1,1′- (*C*)		258(4·57), 266(4·58)	297(4·07)	350(3·74)
3,3′-	-2,2′- (*D*)	221(4·77)	269(4·68)	305(4·11)	355(3·75)
Binaphthyls [18]					
1,1′-		220(4·95)		283(4·12), 293(4·10)	
1,2′-		219(5·10)		282(4·20)	
2,2′-		212(4·65)		254(5·0)	
Nitronaphthalenes [19]					
2-			258(4·40)	306(3·93)	352(3·44)
1-			243(4·02)		343(3·60)
1′,2-Diamino-1,2′-binaphthyl			244(3·74)	283(4·09), 293(4·04)	335(3·92)
2,2′-Diamino-1,1′-binaphthyl [17]			241(4·97)	{ 273(4·08), 282(4·14), 293(4·02) †	346(3·75)
2-Naphthylamine [17]			236(4·78)	280(3·82), 292(3·73)	340(3·28)

† Inflexion.

It is interesting that 3,3′-dinitro-2,2′-binaphthyl exhibits a large amount of steric hindrance whilst 1,1′-dinitro-2,2′-binaphthyl is unhindered. Steric models (Catalin) indicate that, while a completely planar structure for 1,1′-dinitro-2,2′-binaphthyl is unlikely, the hindrance between the 1-nitro-group and the 8-hydrogen atom will rotate the nitro-group out of the plane of the ring, thus allowing the two naphthalene systems to become nearly coplanar. In 3,3′-dinitro-2,2′-dinaphthyl, however, the nitro-groups' being in the plane of the aromatic ring leads to more steric hindrance and it may be that it is energetically more favourable for the nitro-group to be in this planar position rather than that the binaphthyl itself should become more planar. However, it is well known that the onset of spectrally detectable effects occurs somewhere between the covalent and the van der Waals distances (cf. Braude [16]) and so different types of model can give different results.

Jones [17] found that the ultraviolet spectrum of 2,2′-diamino-1,1′-binaphthyl closely resembled that of 2-naphthylamine, indicating little conjugation between the naphthalene nuclei. This parallels the case of the above dinitrobinaphthyls, and again the unsymmetrical 1′,2-diamino-1,2′-binaphthyl shows rather less fine structure than the more sterically hindered, symmetrical 2,2′-diamino-1,1′-binaphthyl (Table 2).

EXPERIMENTAL

Preparation of 2-Nitro-1-naphthylamine from Naphthionic Acid (With C. D. JOHNSON).—Naphthionic acid (5 g.), pyridine (2·25 g.), and acetic anhydride (9·5 g.) were refluxed together for 1 hr. After cooling to *ca.* 40° hydrochloric acid (*d* 1·18; 25 c.c.) in water (10 c.c.) was added with stirring. Precipitation of 4-acetamidonaphthalene-1-sulphonic acid began immediately and next morning it was collected, washed with acetic acid, and dried at 100°. The yield is

[16] Braude in "Progress in Stereochemistry," Vol. I, ed. Klyne, Butterworths, London 1954, p. 146.
[17] Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127.
[18] Friedel and Orchin, "Ultra-violet Spectra of Aromatic Compounds," Wiley and Sons, New York, 1951.
[19] Coulson, Thesis, London, 1955.

almost quantitative and the product gave a satisfactory assay with N-sodium hydroxide (phenolphthalein as indicator). It is essential at this stage to have a very fine crystalline material, otherwise the subsequent nitration is extremely difficult.

The acetyl derivative (5 g.) was suspended in acetic acid (10 c.c.), and nitric acid (*d* 1·5; 2·5 g.) was added together with boron trifluoride–acetic acid complex (20 g.; 40% of BF_3) in acetic acid (75 c.c.). A crystal of sodium nitrite was added and, with very good stirring, the temperature was raised to 75° and maintained there for 30 min. (at lower temperatures nitration was incomplete, whereas at 80° large amounts of by-products were produced). Yields varied from 40 to 70%.

The nitro-amide (10 g.) was refluxed with a 1 : 1 : 1 v/v mixture (300 c.c.) of ethanol, water, and sulphuric acid (*d* 1·84) for 30 min. Any solids remaining at this stage were filtered off and the filtrate was poured on ice. The solids were collected, washed with water, and basified by further trituration with water, yielding almost pure 2-nitro-1-naphthylamine (*ca.* 70%; overall from naphthionic acid 30—50%). Very pure material may be obtained by chromatographing this product (in 5 g. portions) on alumina in benzene.

Crossed Ullmann Reaction between 1-*Iodo*-2-*nitronaphthalene and* 2-*Iodo*-1-*nitronaphthalene.*—The iodo-compounds were prepared by diazotising the amines by Hodgson and Walker's method,[20] and decomposing the diazonium solutions by addition to aqueous potassium iodide and iodine. The yields of almost pure material (which were used directly without recrystallisation) were 80 and 98% respectively. The intimately mixed iodo-compounds (5 g. of each) were heated at 155° in a constant-temperature heater, and copper bronze (8 g.) was added slowly with stirring. The inner vessel was occasionally removed and allowed to cool to 150° before replacement, to prevent the temperature of the mixture from exceeding 175°. Heating was then continued for 1 hr. The cooled solids were extracted with boiling benzene (3 × 100 c.c.), and the extracts concentrated and filtered through alumina (2·5 × 20 cm.). Further concentration and cooling yielded 1,1′-dinitro-2,2′-binaphthyl (*A*) (0·15 g., 2·6%), m. p. 283° (Cumming and Howie [21] give m. p. 284°). The remainder of the benzene was evaporated, yielding a semicrystalline material which was stirred with light petroleum (b. p. 60—80°) (15 c.c.) and benzene (6 c.c.); filtration yielded 1′,2-*dinitro*-1,2′-*binaphthyl* (*B*) (2·3 g., 40%, m. p. 170—172°). Crystallised from 1 : 1 v/v ethanol–ethyl acetate this had m. p. 174—176° (Found: C, 70·1; H, 3·6; N, 8·1. $C_{20}H_{12}O_4N_2$ requires C, 69·8; H, 3·5; N, 8·1%). Concentration of this mother-liquor gave further amounts of compound (*A*) (0·15 g., 2·6%). Evaporation of the original mother-liquor gave a tar from which nothing crystallised. Compound (*B*) was orientated by the fact that it was different from both (*A*) and 2,2′-dinitro-1,1′-binaphthyl (mixed m. p.s., ultraviolet and infrared spectra).

1′,2-*Diamino*-1,2′-*binaphthyl.*—1′,2-Dinitro-1,2′-binaphthyl (1 g.) in ethanol (10 c.c.) and ethyl acetate (100 c.c.), containing B.D.H. stabilised Raney nickel (1 g.), was reduced with hydrogen at 70—80° (atmospheric pressure). Reduction appeared to be complete in about 12 hr. Then the nickel was filtered off and the filtrate concentrated to 20 c.c. The crude diamine was collected and crystallised three times from ethanol, giving white needles (0·71 g., 86%), m. p. 149° (Cook *et al.*[3] give 150—151°) (Found: C, 83·2; H, 5·7; N, 9·2. Calc. for $C_{20}H_{16}N_2$: C, 84·5; H, 5·6; N, 9·9%).

Preparation and Pyrolysis of 1,2′-*Dinaphthyl*-1′,2-*iodonium Iodide.*—The above diamine (1 g.) was dissolved in warm water (15 c.c.) and hydrochloric acid (*d* 1·18; 8 c.c.). This was treated, at 0°, with sodium nitrite (0·6 g.) in water (4 c.c.) and after 15 min. added to potassium iodide (9 g.) and iodine (2 g.) in water (4 c.c.). After 2 hr. the solids were collected, washed with water, and kept overnight in aqueous 10% (w/v) sodium thiosulphate; the semiliquid product solidified. This crude product (2·1 g.) was used for pyrolyses which were carried out as described by Ward and Pearson.[1]

1-*Amino*-2,2′-*azonaphthalene and* 4-*Amino*-1,2′-*azonaphthalene.*—These compounds were prepared by coupling diazotised 2-naphthylamine with 1-naphthylamine hydrochloride in water at pH 3·5, with subsequent chromatographic separation of the mixed azo-dyes.[6] 1-*Amino*-2,2′-*azonaphthalene* was obtained as red plates [from 1 : 1 v/v benzene–light petroleum (b. p. 60—80°)], m. p. 193—194° (Found: C, 81·2; H, 5·3; N, 13·6. $C_{20}H_{16}N_2$ requires C, 80·8; H, 5·1; N, 14·1%), and 4-amino-1,2′-azonaphthalene as orange-red needles (from the same solvents), m. p. 144—145° (cf. m. p. 152°, Nietzki and Gottig; [4] 136°, Cook *et al.*[3]).

[20] Hodgson and Walker, *J.*, 1933, 1620.
[21] Cumming and Howie, *J.*, 1931, 3176.

Deamination of 4-Amino-1,2′-azonaphthalene.—The azo-compound (5 g.) was dissolved in warm ethanol (250 c.c.), the solution cooled to 0°, and sulphuric acid (*d* 1·84; 8·5 c.c.) added. Sodium nitrite (1·16 g., 1 mol.) in water (5 c.c.) was slowly added, at 0°, and the mixture allowed to warm to room temperature, nitrogen being evolved. After 72 hr. the mixture was poured into water (1 l.), and the solid collected and dried *in vacuo* at 70°. This was extracted with light petroleum (b. p. 60—80°) (200 c.c., Soxhlet), and the extract concentrated to 50 c.c. and filtered through alumina (3 × 20 cm.). From the filtrate almost pure 1,2′-azonaphthalene (1·9 g., 40%) was obtained, forming orange needles (from ethanol), m. p. 143—144° (Badger and Lewis [5] give 145°). Similar yields were obtained when the mixed azo-dyes were deaminated. Deamination by diazotisation in a mixture of sulphuric and hypophosphorous acid gave only 27% yield. Hodgson–Walker diazotisation followed by addition of cuprous oxide, or addition to methanol–cuprous oxide, did not give this product.

Preparation and Rearrangement of 1,2′-Hydrazonaphthalene.—1,2′-Azonaphthalene (1 g.) was dissolved in refluxing acetone (85 c.c.), and the hot solution was treated with zinc powder ("AnalaR," 1·5 g.) and ammonia (*d* 0·88; 15 c.c.). After 15 minutes' refluxing, this treatment was repeated and in a further 10 min. the solution was colourless. The solution was filtered hot to remove zinc, the zinc was extracted by hot acetone (15 c.c.), and the combined filtrates were cooled in a closed vessel to minimise oxidation. Hydrochloric acid (*d* 1·8) was then added (until the pH was $\not>2$) and after 3 hr. at room temperature the solution was basified by ammonia (*d* 0·88). The 1′,2-diamino-1,2′-binaphthyl slowly separated and after 24 hr. was collected as a white solid (0·95 g., 95%; m. p. 137—140°); crystallised from ethanol it had m. p. 149° and was identical (ultraviolet spectra) with the diamine prepared as above.

Ultraviolet spectra were recorded by a Unicam S.P. 500 photoelectric spectrophotometer for ethanol solutions. The infrared spectra of the four dinitrobinaphthyls will be made available through the Documentation of Molecular Spectroscopy punched-card collection.

The authors are indebted to the Department of Scientific and Industrial Research for a special grant and to Dr. D. H. Whiffen (University of Birmingham) for the infrared spectral measurements.

LEICESTER COLLEGE OF TECHNOLOGY AND COMMERCE,
LEICESTER.

[*Received, April 15th*, 1959.]

---

684. *Steric Effects in 2,2′-Bridged Diphenyls with a Heterocyclic Bridging Ring. Part II.* An Optically Active Tetrahydrodibenzazocine.*

By SHAKTI R. AHMED and D. MURIEL HALL.

1,2,7,8-Tetrahydro-3,4:5,6-dibenzazocine-1-spiro-1′-piperidinium picrate has been synthesised and obtained in optically active forms by crystallisation of the (+)- and (−)-α-bromocamphor-π-sulphonates. The compound is optically highly labile; Arrhenius parameters for racemisation have been determined. The optical stabilities of this and other 2,2′-bridged diphenyls are discussed.

THE optical stabilities of a number of diphenyls, in which two or three atoms join the 2- and the 2′-position to form part of a six- or seven-membered ring, have now been investigated.[1-7] In most of these compounds additional substituents (or parts of fused benzene rings) are present in the diphenyl 6- and 6′-positions.[3-7]

Chemical differences among the compounds studied have precluded comparisons of

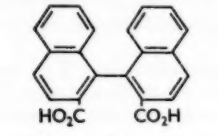
* Part I, *J.*, 1958, 3043.

[1] Iffland and Siegel, *J. Org. Chem.*, 1956, **21**, 1056; *J. Amer. Chem. Soc.*, 1958, **80**, 1947.
[2] Truce and Emrick, *ibid.*, 1956, **78**, 6130.
[3] Beaven, Hall, Lesslie, and Turner, *J.*, 1952, 854.
[4] Hall and Turner, *J.*, 1955, 1242; Hall, *J.*, 1956, 3674.
[5] Armarego and Turner, *J.*, (*a*) 1956, 3668; (*b*) 1957, 13.
[6] Badger, Jefferies, and Kimber, *J.*, 1957, 1837.
[7] Ahmed and Hall, *J.*, 1958, 3043.

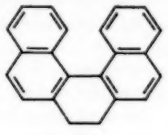
XUM

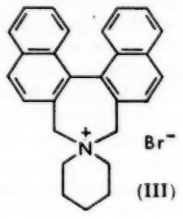
optical stability under identical conditions but it is nevertheless possible to make certain generalisations.

(1) In the few cases [4,5,6] where reasonably valid comparisons can be made the bridged diphenyls (with a 6- or 7-membered ring) are optically *less* stable than unbridged compounds with somewhat similar blocking groups, presumably because the molecules of the bridged compound are held in a position which is already part of the way towards the transition state for racemisation. For example, compound (I) is optically more stable than (II) or (III) [4]; (IV) than (V); [5a] and (VI),[8] apparently, than (VII).[7] It is not, of

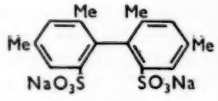


(I)

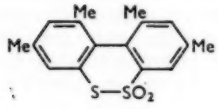

(II)



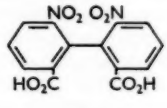
(III)



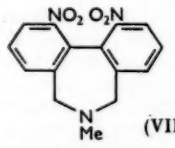
(IV)



(V)



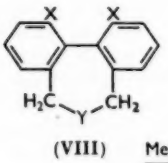
(VI)



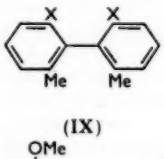
(VII)

course, possible to make a direct comparison; even if both (VIII) and (IX) happen to be available in optically active forms (the ditolyl being more suitable than the diphenic acid), the unbridged compound may racemise by either of two paths; in one of these, like groups pass each other (as indicated in IX), and in the other, unlike groups pass each other (as indicated in X). [In the case of (XI) [9] the second type of racemisation path is almost certainly the more important and, in fact, this compound is optically less stable than (XII) [3].] Further, the optical stability of (VIII) is undoubtedly influenced by the nature of the atom Y and by groups which may be attached to it.

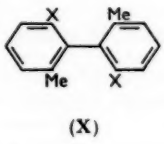
(2) Where both 6- and 7-membered ring compounds (with the same 6,6′-substituents) have been studied, the 6-membered ring compound is of a considerably lower optical stability than the 7-membered ring compound.[4,5b]



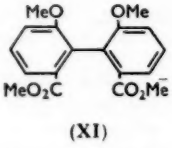
(VIII)



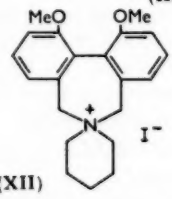
(IX)



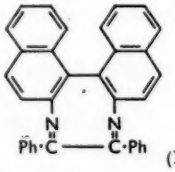
(X)



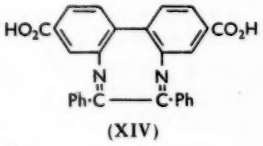
(XI)



(XII)



(XIII)

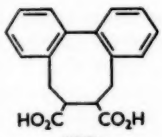


(XIV)

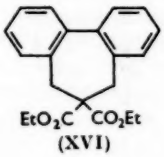
This suggested to us that compounds in which the bridge forms part of an 8-membered ring might be of yet higher optical stability. For some years such compounds showing optical activity were limited to two with an unsaturated heterocyclic bridge. Kuhn and Goldfinger [10] prepared the enantiomeric forms of the pentacyclic compound (XIII) from

[8] Kuhn and Albrecht, *Annalen*, 1927, **455**, 272.
[9] Wittig and Petri, *ibid.*, 1933, **505**, 17.
[10] Kuhn and Goldfinger, *ibid.*, 1929, **470**, 183.

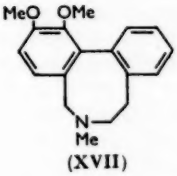
(+)- and (−)-2,2′-diamino-1,1′-dinaphthyl, and Bell [11] resolved the analogue (XIV), in which the 6- and the 6′-position are occupied only by hydrogen. In 1957 Mislow [12] obtained the two dibenzocyclo-octadiene acids (XV) in optically active forms and found that both compounds were optically highly labile, the *cis*-acid racemising and the *trans*-acid mutarotating at 31·5° in ethanolic solution with half-lives of 85 min. and 12 min. respectively.[13] They are thus of the same order of optical stability as the 7-membered ring homocyclic compound [1] (XVI) which has a half-life of 80 min. in cyclohexane at 32·5°. Bell's compound, however, is optically much more stable (undergoing resolution, not asymmetric transformation) and this may be attributed to the greater rigidity conferred on the molecule by the additional double bonds.



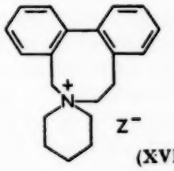
(XV)



(XVI)



(XVII)



(XVIII)

The recent synthesis of *OO*-dimethylapogalanthamine (XVII) by Kobayashi and Uyeo [14] provided a route to a heterocylic compound with an 8-membered ring. In the present work 2-(2-bromoethyl)-2′-bromomethyldiphenyl was prepared and condensed with (−)-ephedrine. Crystallisation of the quaternary iodide gave strong evidence of optical resolution but not of optical lability (at room temperature). The presence of a new asymmetric nitrogen atom is a complicating factor and, in view of this and of the initial low yield of the quaternary iodide, this compound was not investigated further.

Condensation of the dibromo-compound with piperidine gave a quaternary compound (XVIII), isolated as the iodide. The (+)-α-bromocamphor-π-sulphonate underwent asymmetric transformation by crystallisation, 93% of the salt crystallising as one diastereoisomer, which underwent rapid mutarotation in solution (*e.g.*, it had a half-life of about 3 min. in acetonitrile solution at 15·5°). The bromocamphorsulphonate and the iodide had similar solubilities in cold ethanol so that it was not possible to reprecipitate the iodide. However, the picrate was less soluble and accordingly the bromocamphorsulphonate was dissolved in ethanol at −10° and treated with a cold (−10°) saturated ethanolic solution of picric acid; (−)-1,2,7,8-tetrahydro-3,4:5,6-dibenzazocine-1-spiro-1′-piperidinium picrate [XVIII; $Z = C_6H_2(NO_2)_3O$] separated. (A preliminary account of this part of the work has already appeared.[15]) In order to obtain the other enantiomer the (−)-α-bromocamphor-π-sulphonate was prepared. Similar cold decomposition gave the (+)-picrate.

Racemisation of the optically active picrates was studied in acetone solution at 2° (half-life 24·5 min.), 10°, 16°, and 23° (half life 1·4 min.). The activation energy is 22·1 kcal. mole^{-1} and the non-exponential term A of the Arrhenius equation is $10^{14\cdot2}$ sec.$^{-1}$. The racemisation rate was also determined in acetonitrile at 2° and was, within experimental error, the same as in acetone at that temperature. It was not possible to determine the rate in ethanol as the solubility of the picrate in cold ethanol was too low.

The dibenzazocine compound is thus even less optically stable than Mislow's acids. The replacement of a carbon atom in the ring by the smaller positive nitrogen may be partly responsible for this, but the complexity of the factors contributing to optical stability

[11] Bell, *J.*, 1952, 1527.
[12] Mislow, *Trans. New York Acad. Sci.*, 1957, **19**, 298.
[13] Dvorken, Smyth, and Mislow, *J. Amer. Chem. Soc.*, 1958, **80**, 486.
[14] Kobayashi and Uyeo, *J.*, 1957, 638.
[15] Ahmed and Hall, *Chem. and Ind.*, 1958, 1329.

XUM

is clearly indicated by the Arrhenius parameters for the racemisation of Mislow's *cis*-acid in different solvents.[13] In ethanol E is 22·8 kcal. mole^{-1} and A is $10^{12\cdot5}$ sec.$^{-1}$; in 2·32N-sodium hydroxide, however, E is 25·4 kcal. mole^{-1} and A is $10^{14\cdot6}$ sec.$^{-1}$. Thus if our dibenzazocine compound in acetone is compared with the acid in ethanol, the greater optical stability of the latter is due mainly to its smaller value of A but, if the comparison is made with the acid in sodium hydroxide, then the greater optical stability of the homocyclic compound is largely the result of its higher activation energy. The picrate, like the acid in sodium hydroxide, will of course be ionised but in acetone it will not necessarily be highly dissociated.

de la Mare [16] and Harris [17] have recently drawn attention to the fact that the value of A for racemisation of diphenyls is often of the order of 10^{11} sec.$^{-1}$. In Harris's Table [18] (which includes various types of internally hindered compounds) values of A in the range 10^{13} to 10^{14} sec.$^{-1}$ are shown by two bridged compounds (II and IV) and by tri-*o*-thymotide. Since Mislow's *cis*-acid, the dibenzazocine compound, and 4′,1″-difluoro-2,7-dihydro-1-methyl-3,4:5,6-dibenzazepine (A $10^{12\cdot7}$ sec.$^{-1}$) also have values of A of *ca.* 10^{13} sec.$^{-1}$ it seems possible that the two types of diphenyl, bridged and non-bridged, fall roughly into two classes as far as the non-exponential term in the Arrhenius equation is concerned. At present the information available is quite inadequate to decide whether the greater optical stability of the non-bridged compounds is due solely to the different range of values of A or whether, as surmised earlier in this paper, the non-bridged compounds do in general also have lower activation energies.

Compound (VII) with A $10^{11\cdot5}$ sec.$^{-1}$ is apparently an exception to this classification. Brooks, Harris, and Howlett [19] found, however, that the introduction of further nitro-groups into 6-nitrodiphenic acid increased the optical stability of the compound by reducing A without altering E and it is possible that the nitro-groups in compound (VII) are having a similar effect.

Experimental

(In all polarimetric readings $l = 2$.)

Rates of racemisation and mutarotation were determined by dissolving the finely ground solid as quickly as possible in solvent at approximately the right temperature and filtering the solution into a jacketted polarimeter tube round which water at the required temperature was circulating.

Methyl 2′-Carbomethoxymethyldiphenyl-2-carboxylate.—Diphenic anhydride (m. p. 225—226°) * was converted into methyl hydrogen diphenate,[21] and an Arndt–Eistert reaction carried out [22] on the acid chloride of the latter, with methanol as solvent for the decomposition of the diazo-ketone. The resulting ester was dimorphic (needles and prisms), both forms having the same m. p. (71—72°).

2-(2-Hydroxyethyl)-2′-hydroxymethyldiphenyl was obtained by reducing the above ester in ethereal solution with lithium aluminium hydride. It had m. p. 103·5—104° (from benzene) (Found: C, 79·1; H, 7·0. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·1%).

1,2,7,8-Tetrahydro-3,4:5,6-dibenzazocine-1-spiro-1′-piperidinium Iodide (XVIII; Z = I).—The above diol (12 g.) was heated with 48% hydrobromic acid (570 c.c.) for ½ hr. at 126°. The acid was then decanted; another 570 c.c. of acid was added to the residue and the mixture was heated for a further ½ hr. The mixture was cooled and the acid again decanted. The residual dibromo-compound, which did not solidify, was dissolved in benzene and dried (Na_2SO_4). Piperidine (13 c.c., 2·3 mols.) was added and the solution kept at *ca.* 50° for 6 hr.

* The highest m. p. given in the literature [20] is 222—224°; most references are to values below 220°.

[16] de la Mare, "Progress in Stereochemistry," Vol. I (Ed. Klyne), Butterworths, London, 1954.
[17] Harris, *ibid.*, Vol. II (Ed. Klyne and de la Mare), Butterworths, London, 1958, p. 173.
[18] Ref. 17, p. 174.
[19] Brooks, Harris, and Howlett, *J.*, 1957, 1934.
[20] Underwood and Kochmann, *J. Amer. Chem. Soc.*, 1923, **45**, 3071.
[21] *Idem, ibid.*, 1924, **46**, 2069.
[22] Marvel and Patterson, *ibid.*, 1941, **63**, 2218.

Solid separated and was filtered off and washed with warm benzene. It was very soluble and was therefore converted into the iodide by treating the cold aqueous solution with a saturated solution of potassium iodide. The quaternary *iodide*, crystallised from water, had m. p. 248° decomp. (7·5 g., 36%) (Found: C, 59·3; H, 6·5; N, 3·05; I, 31·5. $C_{20}H_{24}NI$ requires C, 59·3; H, 6·0; N, 3·5; I, 31·3%).

(−)-1,2,7,8-*Tetrahydro*-3,4:5,6-*dibenzazocine*-1-*spiro*-1′-*piperidinium* (+)-α-*Bromocamphor*-π-*sulphonate*.—The quaternary iodide (3·0 g.) was treated with silver (+)-bromocamphorsulphonate (3·1 g.) in aqueous alcohol. The filtered solution was evaporated to dryness and the residue was dissolved in a mixture of ethanol and ethyl acetate. 3·5 g. of salt gradually crystallised and another 0·5 g. of the same diastereoisomer was obtained from the mother-liquor (total yield 93%). The same diastereoisomer was obtained by crystallisation from acetonitrile. The (−)-dibenzazocine-1-spiro-1′-piperidinium (+)-α-bromocamphor-π-sulphonate had m. p. 201°, initial $[\alpha]_{5461}^{15·5}$ +2·3° (by extrapolation) and final $[\alpha]_{5461}^{15·5}$ +64·6° (*c* 0·747 in acetonitrile).

The mutarotation of this salt was studied (*a*) in ethanol at 7° (*c* 1·046), α_{5461} changing from +0·87° to +1·35° ($k = 8·5 \times 10^{-4}$ sec.$^{-1}$), and (*b*) in acetonitrile at 15·5° (*c* 0·747), α_{5461} changing from +0·325° to +0·97° ($k = 3·5 \times 10^{-3}$ sec.$^{-1}$).

(+)-1,2,7,8-*Tetrahydro*-3,4:5,6-*dibenzazocine*-1-*spiro*-1′-*piperidinium* (−)-α-*Bromocamphor*-π-*sulphonate*.—This was obtained by using the quaternary iodide (0·9 g.) and silver (−)-α-bromocamphor-π-sulphonate (0·95 g.). 1·15 g. of the *salt* (88%) crystallised as one diastereoisomer and had initial $[\alpha]_{5461}^{15·5}$ −4·0° (by extrapolation) and final $[\alpha]_{5461}^{15·5}$ −65·1° (*c* 0·914 in acetonitrile) (Found: C, 60·9; H, 6·5. $C_{30}H_{38}O_4NBrS$ requires C, 61·2; H, 6·5%).

The mutarotation of this salt was studied in acetonitrile at 15·5° (*c* 0·914). α_{5461} changed from −0·53° to −1·19°; $k = 3·7 \times 10^{-3}$ sec.$^{-1}$. (Average *k* for the two isomers $3·6 \times 10^{-3}$ sec.$^{-1}$.)

(−)-1,2,7,8-*Tetrahydro*-3,4:5,6-*dibenzazocine*-1-*spiro*-1′-*piperidinium Picrate*.—The finely ground (+)-bromocamphorsulphonate was dissolved in ethanol, precooled to −10°, and a saturated ethanolic solution of picric acid at −10° added to it. The (−)-picrate began to separate on scratching and was rapidly filtered and dried *in vacuo*. It racemised rapidly in solution and had initial $[\alpha]_{5461}^{2}$ −71° in acetone (by extrapolation to zero time) and initial $[\alpha]_{5461}^{2}$ −75° in acetonitrile.

(+)-1,2,7,8-*Tetrahydro*-3,4:5,6-*dibenzazocine*-1-*spiro*-1′-*piperidinium Picrate*.—Similar treatment of the (−)-bromocamphorsulphonate with picric acid at −10° gave the (+)-*picrate*, which had initial $[\alpha]_{5461}^{10}$ +62° in acetone (by extrapolation). For analysis a sample was crystallised from ethanol; it was then presumably racemic and had m. p. 196—197° (Found: C, 62·1; H, 5·0; N, 11·5. $C_{26}H_{26}O_7N_4$ requires C, 61·65; H, 5·2; N, 11·1%).

Racemisation of (−)- *and* (+)-1,2,7,8-*Tetrahydro*-3,4:5,6-*dibenzazocine*-1-*spiro*-1′-*piperidinium Picrates*.—Racemisation rates were measured in acetone solution, two determinations being made at each temperature (*c* 0·4—0·8; observed α_{5461} at first reading between 0·7° and 0·4°). At 2° $k = 4·7 \times 10^{-4}$ sec.$^{-1}$; at 10° $k = 1·33 \times 10^{-3}$ sec.$^{-1}$; at 16° $k = 3·3 \times 10^{-3}$ sec.$^{-1}$; at 23° $k = 8·45 \times 10^{-3}$ sec.$^{-1}$; whence $E = 22·1$ kcal. mole^{-1}, and $A = 10^{14·2}$ sec.$^{-1}$. The rate was also determined in acetonitrile solution at 2° and gave $k = 4·8 \times 10^{-4}$ sec.$^{-1}$.

1,2,7,8-*Tetrahydro*-1-(β-*hydroxy*-α-*methylphenethyl*)-1-*methyl*-3,4:5,6-*dibenzazepinium Iodide*.—A solution in dry benzene of the dibromo-compound (from 15 g. of the diol) and (−)-ephedrine (from 26 g. of the hemihydrate) was kept at 50—60° during 40 hr.; the quaternary compound formed was extracted with water and precipitated as the *iodide* (4 g., 15%). After crystallisation from ethanol it had m. p. 224—225° (decomp.) (Found: C, 61·5; H, 6·15; I, 26·0. $C_{25}H_{28}ONI$ requires C, 61·9; H, 5·8; I, 26·15%). By controlled crystallisation from aqueous alcohol two fractions were obtained with $[\alpha]_{5461}^{15}$ +118° (*c* 0·214 in ethanol) and $[\alpha]_{5461}^{15}$ −60° (*c* 0·226 in ethanol) respectively. Their rotations were unchanged after their ethanolic solutions had been kept at 100° for 3 hr.

We thank our colleagues, and especially Dr. M. M. Harris, for many helpful discussions and Mr. R. K. Mitchell for technical assistance. We also thank Imperial Chemical Industries Limited for a grant and the University of Aligarh for study leave (to S. A.).

Bedford College, University of London,
Regent's Park, London, N.W.1.

[*Received, April 17th*, 1959.]

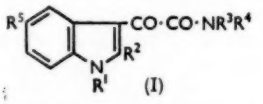
685. *The Synthesis of Some Indolylalkylamines.*

By (Mrs.) A. F. Ames, D. E. Ames, C. R. Coyne, T. F. Grey, I. M. Lockhart, and R. S. Ralph.

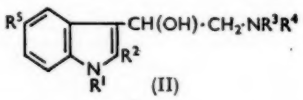
A series of 3-indolylalkylamines and a number of their derivatives have been prepared for pharmacological study. Most of these compounds were obtained by reduction of intermediates prepared by the action of oxalyl chloride and then secondary amines on indoles by addition of nitrostyrenes to indoles, or by reactions of substituted gramines. Grignard reagents with *NN*-dialkyl-3-indolylglyoxylamides give high yields of α-substituted glycollamides. The methylation of some 3-indolylalkylamine derivatives with formic acid–formaldehyde and with methyl iodide–sodamide has been examined.

This paper describes the synthesis of a number of substituted 3-indolylalkylamines and related compounds for pharmacological study.

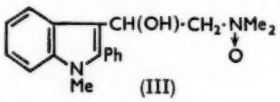
It has been shown [1,2,3] that oxalyl chloride condenses readily with indoles to give 3-indolylglyoxylyl chlorides which can be converted into the corresponding amides. This method has been used to prepare a number of 1,2-disubstituted 3-indolylglyoxylamides (I) (Table 1, p. 3393) which have been reduced with lithium aluminium hydride to the hydroxy-amines (II) (Table 2, p. 3394) by Speeter and Anthony's method.[2,4] The primary amine (II; $R^1 = Me$, $R^2 = Ph$, $R^3 = R^4 = R^5 = H$) could not be obtained satisfactorily in this manner but was prepared from the dibenzylamine (II; $R^1 = Me$, $R^2 = Ph$, $R^3 = R^4 = CH_2Ph$, $R^5 = H$) by catalytic debenzylation. Oxidation of hydroxy-amine (II; $R^1 = R^3 = R^4 = Me$, $R^2 = Ph$, $R^5 = H$) with perbenzoic acid gave the *N*-oxide (III).



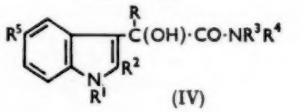
(I)



(II)



(III)



(IV)

It was found that the α-keto-amides (I) with Grignard reagents gave the hydroxy-amides (IV) in good yield. Attempts to use phenyl-lithium in this reaction were unsuccessful although phenylmagnesium bromide gave a product of type (IV). The amides (IV) were also reduced with lithium aluminium hydride, to the corresponding hydroxy-amines (V).

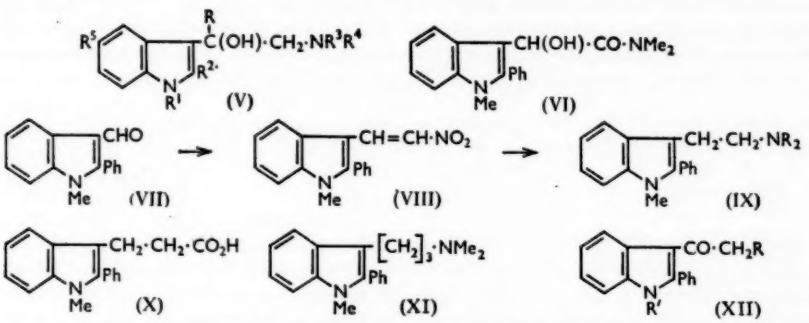
The keto-amide (I; $R^1 = R^3 = R^4 = Me$, $R^2 = Ph$, $R^5 = H$) was reduced with potassium borohydride to *NN*-dimethyl-α-(1-methyl-2-phenyl-3-indolyl)glycollamide (VI), but attempts to convert this into the α-chloro-amide, which it was hoped to reduce to amine (IX; R = Me), were unsuccessful. As an alternative route to (IX; R = Me), 1-methyl-2-phenylindole was formylated, by the phosphorus oxychloride–dimethylformamide method;[5] condensing the resulting aldehyde (VII) with nitromethane[6] gave

[1] Kharasch, Kane, and Brown, *J. Amer. Chem. Soc.*, 1940, **62**, 2242.
[2] Speeter and Anthony, *ibid.*, 1954, **76**, 6208; Speeter, U.S.P. 2,825,734; Speeter and the Upjohn Co., B.P. 797,258.
[3] Shaw, McMillan, Gudmondson, and Armstrong, *J. Org. Chem.*, 1958, **23**, 1171.
[4] The Upjohn Co., B.P. 778,823 and 797,258.
[5] Smith, *J.*, 1954, 3842; Silverstein, Ryskiewicz, and Chaikin, *J. Amer. Chem. Soc.*, 1954, **76**, 4485.
[6] Burger, Stein, and Clements, *J. Org. Chem.*, 1957, **22**, 143; cf. Young, *J.*, 1958, 3493; Ash and Wragg, *J.*, 1958, 3887.

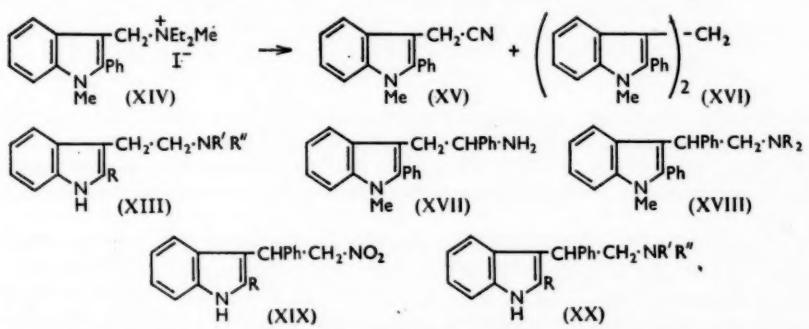
the nitro-compound (VIII) which was reduced with lithium aluminium hydride to 1-methyl-2-phenyl-3-indolylethylamine (IX; R = H). Methylation by catalytic hydrogenation in the presence of formaldehyde gave the tertiary amine (IX; R = Me). Addition of ethylene oxide to amine (IX; R = H) yielded *NN*-di-2′-hydroxyethyl-2-(1-methyl-2-phenyl-3-indolyl)ethylamine (IX; R = $CH_2 \cdot CH_2 \cdot OH$).

For the synthesis of the homologous amine (XI), the aldehyde (VII) was condensed with ethyl cyanoacetate,[7] the resulting cyano-ester was hydrogenated and hydrolysed to β-(1-methyl-2-phenyl-3-indolyl)propionic acid (X), the dimethylamide of which was reduced by lithium aluminium hydride.

Synthesis of keto-amines (XII; R = NMe_2) was next examined. 1-Methyl-2-phenylindole-3-carboxylic acid was prepared from the oxime of aldehyde (VII) by dehydration with acetic anhydride followed by vigorous alkaline hydrolysis of the resulting nitrile. An attempt to convert this acid through the acid chloride into a chloro-ketone (XII; R′ = Me, R = Cl) by treatment with diazomethane and hydrogen chloride failed. In view of



reports [8] that 1-methylpyrrole can be acylated by using a Grignard reagent and an acyl halide, it was hoped that 1-methyl-2-phenylindole might give the chloride (XII; R′ = Me, R = Cl) on treatment with ethylmagnesium bromide and chloroacetyl chloride, but none could be isolated. When 2-phenylindole was used in these reactions, however, some chloro-ketone (XII; R′ = H, R = Cl) was formed since the action of dimethylamine on the crude product furnished some keto-amine (XII; R′ = H, R = NMe_2).



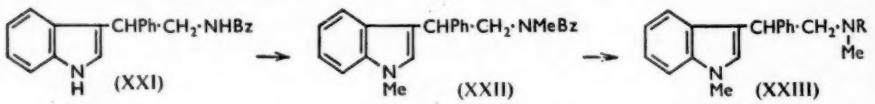
A series of compounds of type (XIII) (Table 3, p. 3394) was prepared from 2-substituted indoles by condensation with oxalyl chloride and reduction of the derived amides with lithium aluminium hydride.[2,9] As with the amides (I), the primary amine (XIII; R = Ph,

[7] Blume and Lindwall, *J. Org. Chem.*, 1946, **11**, 185.
[8] Herz, *ibid.*, 1957, **22**, 1260.
[9] The Upjohn Co., B.P. 781,390.

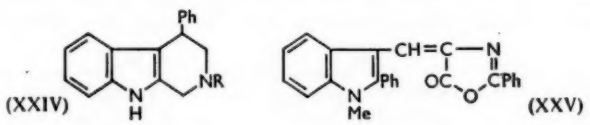
R′ = R″ = H) could not be obtained satisfactorily in this way but was more conveniently prepared by catalytic debenzylation of the tertiary amine (XIII; R = Ph, R′ = R″ = CH_2Ph). When *NN*-diphenyl-α-(2-phenyl-3-indolyl)glyoxylamide (I; $R^1 = R^5 = H$, $R^2 = R^3 = R^4$ = Ph) was reduced with lithium aluminium hydride, the amine was not formed but cleavage of the amide group occurred. The crude products were acetylated and distilled, to give 3-2′-acetoxyethyl-2-phenylindole.

Attention was next turned to the synthesis of compounds with an aryl substituent in the 3-aminoethyl side-chain. The Mannich reaction on 1-methyl-2-phenylindole, followed by treatment with methyl iodide, gave the quaternary salt (XIV) which with potassium silver cyanide [10] yielded mainly the di-indolylmethane (XVI) and only a small yield of nitrile (XV). However, when the salt (XIV) was treated with sodium cyanide in dimethylformamide,[11] the nitrile (XV) was formed in good yield. When this nitrile was allowed to react with phenylmagnesium bromide and then lithium aluminium hydride, 2-(1-methyl-2-phenyl-3-indolyl)-1-phenylethylamine (XVII) was produced in small yield.

For the synthesis of the related amines (XVIII), the addition of nitrostyrene to indoles appeared to provide a convenient approach. Noland and his collaborators [12] have shown that indole and 2-phenylindole with nitrostyrene give adducts (XIX). The nitro-compound (XIX; R = Ph) was catalytically hydrogenated to amine (XX; R = Ph, R′ = R″ = H)



which was converted into the corresponding dimethylamine (XX; R = Ph, R′ = R″ = Me) and other derivatives. Similar reactions starting from 2-*p*-chlorophenylindole and 4-chloro-ω-nitrostyrene were also carried out but attempts to condense ω-nitrostyrene with 1-methyl-2-phenylindole were unsuccessful. *N*-Methylation of amines of type (XX) was therefore examined, experiments being made first with β-3-indolylphenethylamine (XX; R = R′ = R″ = H). The benzoyl derivative (XXI) of this amine was treated with sodamide and methyl iodide in liquid ammonia; the product was shown by the absence of NH bands in the infrared spectrum and by *N*-methyl analysis to be the dimethylated



amide (XXII). Reduction by lithium aluminium hydride then yielded the benzylamine (XXIII; R = CH_2Ph) which was catalytically debenzylated to give *N*-methyl-β-(1-methyl-3-indolyl)phenethylamine (XXIII; R = H). Further methylation of this amine by catalytic hydrogenation in the presence of formaldehyde gave the tertiary amine (XXIII; R = Me).

NN-Dimethyl-β-(1-methyl-2-phenyl-3-indolyl)phenethylamine (XVIII; R = Me) was prepared by a similar sequence of reactions from ω-nitrostyrene and 2-phenylindole.

When the primary amine (XX; R = R′ = R″ = H) was treated with formic acid and formaldehyde, a high-melting crystalline product was obtained. This was formulated as (XXIV; R = CHO) since the infrared spectrum showed the presence of an amide group (intense band at 1657 cm.$^{-1}$ in chloroform). Bader and Oroshnik [13] have discussed the

[10] Snyder, Smith, and Stewart, *J. Amer. Chem. Soc.*, 1944, **66**, 200.
[11] Woodward, Cava, Ollis, Hunger, Daeniker, and Schenker, *ibid.*, 1954, **76**, 4749.
[12] Noland, Christensen, Sauer, and Dutton, *ibid.*, 1955, **77**, 456; Noland and Lange, *ibid.*, 1959, **81**, 1203.
[13] Bader and Oroshnik, *ibid.*, 1957, **79**, 5685.

factors controlling the competition between *N*-methylation and Pictet–Spengler cyclisation of 3-indolylethylamines to tetrahydro-β-carbolines. The isolation of the *N*-formyl compound (XXIV; R = CHO) rather than the *N*-methylamine (XXIV; R = Me) is, however, unexpected. Reduction of the formyl compound with lithium aluminium hydride did give 1,2,3,4-tetrahydro-2-methyl-4-phenyl-β-carboline (XXIV; R = Me).

Finally 1-methyl-2-phenyltryptophan was prepared from the quaternary salt (XIV) and ethyl acetamidomalonate (cf. the synthesis of tryptophan by Snyder and Smith [14]). In an alternative method, 3-formyl-1-methyl-2-phenylindole (VII) was condensed with hippuric acid to give the oxazolone (XXV) but this could not be hydrolysed satisfactorily.

Experimental

2-o-*Chlorophenylindole*.—2-Chloroacetophenone (104 g.), phenylhydrazine (72 g.), and glacial acetic acid (1 c.c.) in ethanol (660 c.c.) were heated under reflux for 8 hr. No crystalline phenylhydrazone could be obtained on cooling; the mixture was evaporated *in vacuo*, the residue was dissolved in toluene (500 c.c.), and the solution evaporated similarly. Zinc chloride (800 g.) was added and the mixture was heated at 180° for 10 min., then poured into 0·3N-hydrochloric acid (3 l.). The mixture was heated on the steam-bath and stirred for 1 hr., cooled to 0°, and filtered, the dark solid being extracted repeatedly with boiling light petroleum (b. p. 80—100°). The *indole* (43 g.) separated as plates, m. p. 86—87° (Found: C, 74·0; H, 4·5; Cl, 15·6. $C_{14}H_{20}NCl$ requires C, 73·8; H, 4·4; Cl, 15·6%).

2-p-*Hydroxyphenylindole*.—4-Hydroxyacetophenone phenylhydrazone (47 g.) was fused with zinc chloride (250 g.), and the product isolated as in the previous example. The crude material was passed in methanol–ether (1 : 20) through a column of aluminium oxide (250 g.). Evaporation of the eluate gave the indole (17 g.) which formed plates, m. p. 227—229°, from benzene (Found: C, 80·6; H, 5·3; N, 6·6. Calc. for $C_{14}H_{11}ON$: C, 80·4; H, 5·3; N, 6·7%). The m. p. (70°) given by Korczynski and Kierzek [15] appears to be erroneous.

2-p-*Methoxyphenylindole*.—Sodium (4·2 g.) in ethanol (650 c.c.) was treated with 2-*p*-hydroxyphenylindole (32·5 g.) and methyl iodide (16·5 c.c.) successively, refluxed for 3 hr., cooled, and filtered; the solid was washed with water and recrystallised from benzene, to give 2-*p*-methoxyphenylindole (21 g.), m. p. 227—228° depressed to 190—195° by the hydroxy-compound (Found: C, 80·9; H, 6·1; N, 6·1. Calc. for $C_{15}H_{13}ON$: C, 80·7; H, 5·9; N, 6·3%). Korczynski and Kierzek [15] give m. p. 228—229°.

2-p-*Benzyloxyphenylindole*.—The hydroxy-compound (37 g.) and benzyl chloride (22 c.c.) were added to sodium ethoxide solution [from sodium (4·6 g.) in ethanol (300 c.c.)], and the mixture was stirred at 90° (bath) for 3 hr., allowed to cool, and filtered. The crude product was washed with water and methanol, then recrystallised from ethyl methyl ketone to give needles of 2-p-*benzyloxyphenylindole* (20 g.), m. p. 243—245° (Found: C, 84·6; H, 5·9; N, 5·0. $C_{21}H_{17}ON$ requires C, 84·3; H, 5·7; N, 4·7%).

2-*Phenethylindole*.—A solution of diazomethane in ether (5 l.) was prepared from methylnitrosourea (300 g.) and cooled below 2° while β-phenylpropionyl chloride (95 g.) in ether (1 l.) was added gradually. After the mixture had been kept for 40 hr., it was cooled below 10° while hydrogen chloride was passed in until 20 min. after evolution of nitrogen had ceased. The ethereal solution was washed with sodium hydrogen carbonate solution and evaporated; the residual chloro-ketone was treated with aniline (150 c.c.) and heated at 120° for 30 min. and then at 180° for 1 hr. The mixture was decomposed with water and ether, and the ethereal layer was washed with 3N-hydrochloric acid (three times) and water, dried ($CaSO_4$–charcoal), filtered, and distilled. 2-*Phenethylindole*, b. p. 160—170°/0·1 mm., solidified rapidly and separated from ethanol as colourless plates, m. p. 123—124° (30 g.) (Found: C, 86·3; H, 6·8; N, 6·4. $C_{16}H_{15}N$ requires C, 86·8; H, 6·8; N, 6·3%).

β-4′-*Benzyloxyphenethylindole*.—By the same procedure as in the previous paragraph, β-*p*-benzyloxyphenylpropionyl chloride [16] (55 g.) was converted into the *indole*, obtained as a

[14] Snyder and Smith, *J. Amer. Chem. Soc.*, 1944, **66**, 350.
[15] Korczynski and Kierzek, *Gazzetta*, 1925, **55**, 361.
[16] Doherty, *J. Amer. Chem. Soc.*, 1955, **77**, 4891.

solid on evaporation of the ethereal solution. Recrystallisation from methanol–ethyl acetate gave plates (11·2 g.), m. p. 163—164° (Found: C, 84·4; H, 6·5; N, 4·3. $C_{23}H_{21}ON$ requires C, 84·4; H, 6·5; N, 4·3%).

1-Methyl-2-phenylindole.—A solution of sodamide was prepared from sodium (20 g.) and liquid ammonia (*ca.* 900 c.c.). 2-Phenylindole (75 g.) was added gradually; the mixture was stirred for 30 min., then treated gradually with methyl iodide (150 g.). After the ammonia had evaporated overnight, water (1·5 l.) was added and the solid was collected, washed with more water, and dried. It was dissolved in benzene (400 c.c.) and light petroleum (1200 c.c.; b. p. 60—80°) was added; the filtered solution was passed through a column of alumina (500 g.). The alumina was washed with the same solvent mixture (1 l.) (2-phenylindole remained strongly adsorbed). Evaporation of the effluent and recrystallisation of the residue from light petroleum (b. p. 80—100°) gave 1-methyl-2-phenylindole (64 g.), m. p. 98—100°. Kissman, Farnsworth, and Witkop [17] give m. p. 100—101°.

The following 1-alkyl-2-arylindoles were prepared similarly: 2-o-*chlorophenyl*-1-*methylindole*, prisms, m. p. 107—108°, from light petroleum (b. p. 60—80°) (Found: C, 74·9; H, 5·0; Cl, 14·8. $C_{15}H_{12}NCl$ requires C, 74·5; H, 5·0; Cl, 14·7%); 2-p-*benzyloxyphenyl*-1-*methylindole*, prisms, m. p. 124—126°, from benzene (Found: C, 83·9; H, 6·1; N, 4·2. $C_{22}H_{19}ON$ requires C, 84·3; H, 6·1; N, 4·5%); 2-*phenyl*-1-*propylindole*, b. p. 175—176°/2·5 mm., n_D^{20} 1·6320 (Found: C, 86·6; H, 7·3; N, 5·8. $C_{17}H_{17}N$ requires C, 86·8; H, 7·3; N, 6·0%); and 5-*methoxy*-1-*methyl*-2-*phenylindole* (from 5-methoxy-2-phenylindole [18]), needles, m. p. 128—129°, from light petroleum (b. p. 60—80°) (Found: C, 81·3; H, 6·2; N, 6·3. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·4; N, 5·9%).

5-Hydroxy-1-methyl-2-phenylindole.—5-Methoxy-1-methyl-2-phenylindole (13 g.) was refluxed for 2·5 hr. with 48% hydrobromic acid (200 c.c.). The mixture was cooled, poured into water (650 c.c.), and filtered; recrystallisation of the solid from aqueous ethanol gave the *hydroxy-indole* (13 g.) as plates, m. p. 150—152° (Found: C, 80·3; H, 5·7; N, 6·4. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·9; N, 6·3%).

5-Benzyloxy-1-methyl-2-phenylindole.—The foregoing hydroxy-indole (16 g.) and benzyl chloride (8·5 c.c.) were added successively to sodium ethoxide solution [from sodium (1·8 g.) and ethanol (110 c.c.)], and the mixture was refluxed for 3·5 hr., poured into water (500 c.c.), and filtered. The solid was washed with water and ether and recrystallised from 2-methoxyethanol to give the *benzyloxyindole* (10 g.), m. p. 159—160° (Found: C, 84·1; H, 6·4; N, 4·5. $C_{22}H_{19}ON$ requires C, 84·3; H, 6·1; N, 4·5%).

3-Indolylglyoxylamides.—A solution of oxalyl chloride (0·13 mol.) in ether (100 c.c.) was cooled in ice-water and stirred while the indole (0·10 mol.) in ether (500 c.c.) was added gradually. After the mixture had been stirred for 1 hr., dimethylamine was passed in until the mixture was alkaline. Stirring was continued for 1 hr. and then water (500 c.c.) was added. The crude product was filtered off and recrystallised (cf. Speeter and Anthony [3]). The *products* are listed in Table I.

2-Amino-1-3'-indolylethanols.—The amide (0·075 mole) in boiling benzene (500 c.c.) was added as rapidly as possible to a stirred suspension of lithium aluminium hydride (10 g.) in ether (500 c.c.). The mixture was refluxed for 3 hr., then treated successively with ethyl acetate (50 c.c.) and 5N-sodium hydroxide solution (15 c.c.). After being refluxed for 1 hr., the solid was filtered off and washed with hot ethyl acetate (500 c.c.), and the combined filtrate and washings were evaporated *in vacuo* to give the crude product which was then recrystallised. For the *products* see Table 2.

When the amide was insoluble in hot benzene, the reduction was carried out in 1,2-dimethoxyethane.

O- and *N*-Benzyl groups in the products were removed by catalytic hydrogenation in ethanol with 5% palladised charcoal.

2-Dimethylamino-1-(1-methyl-2-phenyl-3-indolyl)ethanol N-Oxide.—Perbenzoic acid in chloroform (60 c.c.; 0·315M) was added in portions to the amine (5 g.) in chloroform (50 c.c.) at −20° and the mixture set aside for 15 min. The solution was washed with water (300 c.c.), sodium carbonate solution (5 × 40 c.c.), and water (50 c.c.), dried (Na_2SO_4), and evaporated *in vacuo*. Recrystallisation of the residue from benzene–light petroleum (b. p. 60—80°) furnished the

[17] Kissman, Farnsworth, and Witkop, *J. Amer. Chem. Soc.*, 1952, **74**, 3948.
[18] Terent'ev and Preobrazhenskaya, *Doklady Akad. Nauk S.S.S.R.*, 1957, **114**, 560; *Chem. Abs.*, 1958, **52**, 356.

XUM

TABLE 1. *3-Indolylglyoxylamides* (I).

R¹	R²	R³	R⁴	R⁵	M. p.	Recryst. from	Formula	Found (%) C	H	N	Required (%) C	H	N
Me	Me	Me	Me	H	127—128°	*a*	$C_{14}H_{16}O_2N_2$	69·3	7·0	11·4	68·8	6·6	11·5
Me	Ph	Me	Me	H	198—200	*b*	$C_{19}H_{18}O_2N_2$	75·0	5·9	9·1	74·5	5·9	9·2
Me	*p*-MeC$_6$H$_4$	Me	Me	H	186—187	*b*	$C_{20}H_{20}O_2N_2$	75·1	6·3	8·6	75·0	6·3	8·7
Me	*o*-ClC$_6$H$_4$	Me	Me	H	189—191	*b*	$C_{19}H_{17}O_2N_2Cl$	67·4	5·2	7·6	67·0	5·0	8·2
Me	*p*-ClC$_6$H$_4$	Me	Me	H	215—217	*b*	〃	66·5	5·0	7·8	〃	〃	〃
Me	*p*-PhCH$_2$·O·C$_6$H$_4$	Me	Me	H	175—177	*c*	$C_{26}H_{24}O_3N_2$	76·1	5·8	6·7	75·7	5·9	6·8
Me	Ph	Me	Me	Me	218—220	*b*	$C_{20}H_{20}O_2N_2$	75·0	6·4	8·8	75·0	6·3	8·7
Me	Ph	Me	Me	Cl	214—216	*b*	$C_{19}H_{17}O_2N_2Cl$	67·3	5·1	8·0	67·0	5·0	8·2
Me	Ph	Me	Me	OMe	162—164	*b*	$C_{20}H_{20}O_3N_2$	71·8	5·8	8·7	71·4	6·0	8·3
Me	Ph	Me	Me	O·CH$_2$Ph	173—175	*b*	$C_{26}H_{24}O_3N_2$	75·5	5·8	7·0	75·7	5·9	6·8
Me	Ph	Et	Et	H	141—143	*a*	$C_{21}H_{22}O_2N_2$	75·0	6·3	8·7	75·4	6·6	8·4
Me	*p*-ClC$_6$H$_4$	Et	Et	H	147—148	*b*	$C_{21}H_{21}O_2N_2Cl$	68·9	5·3	7·5	68·4	5·7	7·6
Me	Ph	Et	Pr^n	H	133—135	*b*	$C_{23}H_{24}O_2N_2$	75·9	7·1	8·0	75·8	6·9	8·0
Me	Ph	Et	CH$_2$Ph	H	153—154	*b*	$C_{26}H_{24}O_2N_2$	78·4	6·4	7·1	78·8	6·1	7·1
Me	Ph	Pr^n	Pr^n	H	117—119	*b*	$C_{23}H_{28}O_2N_2$	76·7	7·3	8·0	76·2	7·2	7·7
Me	Ph	CH$_2$Ph	CH$_2$Ph	H	170—171	*d*	$C_{31}H_{28}O_2N_2$	81·0	5·6	6·1	81·2	5·7	6·1
Et	Ph	Me	Me	H	151—153	*b*	$C_{20}H_{20}O_2N_2$	75·1	6·3	9·0	75·0	6·3	8·7
Pr^n	Ph	Me	Me	H	156—157	*b*	$C_{21}H_{22}O_2N_2$	75·8	6·6	8·5	75·4	6·6	8·4
Ph	H	Me	Me	H	95—96	*e*	$C_{18}H_{16}O_2N_2$	73·9	5·7	9·2	74·0	5·5	9·6
Ph	Ph	Me	Me	H	177—179	*b*	$C_{24}H_{20}O_2N_2$	78·0	5·3	8·0	78·2	5·5	7·6
H	Ph	Me	Me	H	213—215	*b*	$C_{18}H_{16}O_2N_2$	73·7	5·7	9·4	74·0	5·5	9·6
H	Ph	Me	CH$_2$Ph	H	173—175	*d*	$C_{24}H_{20}O_2N_2$	77·9	5·5	7·5	78·2	5·5	7·6
H	Ph	–[CH$_2$]$_5$–		H	182—184	*c*	$C_{21}H_{26}O_2N_2$	76·4	5·7	8·2	75·9	6·1	8·4
H	Ph	–[CH$_2$]$_2$·O·[CH$_2$]$_2$–		H	173—175	*c*	$C_{20}H_{24}O_3N_2$	71·3	5·3	8·4	71·8	5·4	8·4
H	*p*-Ph·CH$_2$·O·C$_6$H$_4$	Me	Me	H	177—178	*b*	$C_{25}H_{24}O_3N_2$	75·2	5·6	6·8	75·4	5·6	7·0
H	*p*-MeO·C$_6$H$_4$	Me	Me	H	198—200	*b*	$C_{19}H_{18}O_3N_2$	70·9	5·7	8·7	70·8	5·6	8·7
H	*p*-Ph·CH$_2$·O·C$_6$H$_4$	–[CH$_2$]$_2$·O·[CH$_2$]$_2$–		H	93—94	*f*	$C_{27}H_{24}O_4N_2$ [a]	72·5	5·6	6·1	72·1	5·6	6·2
H	Ph·CH$_2$·CH$_2$	Me	Me	H	123—125	*g*	$C_{20}H_{20}O_2N_2$	74·5	6·2	8·8	75·0	6·3	8·7
H	Ph·CH$_2$·CH$_2$	CH$_2$Ph	CH$_2$Ph	H	160—161	*b*	$C_{33}H_{28}O_2N_2$	80·9	5·8	6·1	81·3	6·0	5·9

[a] Benzene–light petroleum (b. p. 60—80°). [b] Ethanol. [c] Benzene. [d] Chloroform–methanol. [e] Light petroleum (b. p. 80—100°). [f] Methanol. [g] Ether.
[a] 0·5H$_2$O.

TABLE 2. *2-Amino-1-3′-indolylethanols* (II).

R¹	R²	R³	R⁴	R⁵	M. p.	Recryst. from	Formula	Found (%) C	H	N	Required (%) C	H	N
Me	Me	Me	Me	H	110—112°	*a*	$C_{14}H_{20}ON_2$	72·8	8·8	12·0	72·4	8·7	12·1
Me	Ph	Me	Me	H	110—122	*a*	$C_{19}H_{22}ON_2$	77·4	7·6	9·8	77·5	7·5	9·5
Me	*p*-Me·C_6H_4	Me	Me	H	118—119	*a*	$C_{20}H_{24}ON_2$	77·7	7·7	9·1	77·9	7·8	9·1
Me	*o*-ClC_6H_4	Me	Me	H	117—118	*a*	$C_{19}H_{21}ON_2Cl$	69·9	6·4	8·0	69·4	6·4	8·5
Me	*p*-ClC_6H_4	Me	Me	H	157—158	*a*	"	69·4	6·3	8·0	"	"	"
Me	*p*-Ph·CH_2·O·C_6H_4	Me	Me	H	137—139	*b*	$C_{26}H_{26}O_2N_2$	78·2	7·1	7·3	78·0	7·1	7·0
Me	*p*-HO·C_6H_4	Me	Me	H	171—172	*c*, *e*	$C_{19}H_{22}O_2N_2$	73·1	7·2	8·8	73·5	7·1	9·0
Me	*p*-MeO·C_6H_4	Me	Me	H	131—133	*d*, *f*	$C_{20}H_{24}O_2N_2$	74·3	7·5	8·3	74·0	7·5	8·6
Me	Ph	Me	Me	Me	101—102	*a*	$C_{20}H_{24}ON_2$	78·3	7·8	9·2	77·9	7·8	9·1
Me	Ph	Me	Me	Cl	119—121	*a*	$C_{19}H_{21}ON_2Cl$	69·6	6·3	8·8	69·4	6·4	8·5
Me	Ph	Me	Me	OMe	101—103	*a*	$C_{20}H_{24}O_2N_2$	74·7	7·4	8·9	74·0	7·5	8·6
Me	Ph	Me	Me	O·CH_2Ph	121—123	*b*	$C_{26}H_{26}O_2N_2$	77·9	6·9	6·8	78·0	7·1	7·0
Me	Ph	Me	Me	OH	153—155	*d*, *e*	$C_{19}H_{22}O_2N_2$	73·6	7·3	8·7	73·5	7·1	9·0
Me	Ph	Et	Et	H	85—87	*a*	$C_{21}H_{16}ON_2$	78·2	8·1	8·9	78·2	8·1	8·7
Me	*p*-ClC_6H_4	Et	Et	H	131—132	*d*	$C_{21}H_{25}ON_2Cl$	70·8	7·0	7·4	70·7	7·1	7·9
Me	Ph	Et	Pr^n	H	64—65	*a*	$C_{22}H_{28}ON_2$	78·9	8·9	8·2	78·5	8·4	8·3
Me	Ph	Et	CH_2Ph	H	78—79	*a*	$C_{26}H_{28}ON_2$	80·9	7·7	7·2	81·2	7·3	7·3
Me	Ph	Et	H	H	89—91	*a*, *e*	$C_{19}H_{22}ON_2$	77·6	7·6	9·3	77·5	7·5	9·5
Me	Ph	Pr^n	Pr^n	H	67—69	*a*	$C_{23}H_{30}ON_2$	79·1	8·7	8·3	78·8	8·6	8·0
Me	Ph	CH_2Ph	CH_2Ph	H	96—98	*d*	$C_{31}H_{30}ON_2$	82·8	6·6	6·2	83·4	6·8	6·3
Me	Ph	H	H	H	130—132	*a*, *e*	$C_{17}H_{18}ON_2$	76·4	6·4	10·2	76·7	6·8	10·5
Et	Ph	Me	Me	H	118—120	*a*	$C_{20}H_{24}ON_2$	77·6	7·7	8·9	77·9	7·8	9·1
Pr^n	Ph	Me	Me	H	86—87	*a*	$C_{21}H_{26}ON_2$	78·6	8·2	8·5	78·2	8·1	8·7
Ph	H	Me	Me	H	104—105	*a*	$C_{18}H_{20}ON_2$	76·9	7·3	10·1	77·1	7·2	10·0
Ph	Ph	Me	Me	H	148—149	*a*	$C_{24}H_{24}ON_2$	80·9	6·7	8·4	80·9	6·8	7·9

[a] Ethanol. [b] Methanol. [c] Butan-2-one. [d] Aqueous ethanol. [e] Obtained by debenzylation of the preceding compound. [f] Obtained by action of diazomethane on the preceding compound.

TABLE 3. *2-3′-Indolylethylamines* (XIII).

R	R¹	R²	M. p.	Recryst. from	Formula	Found (%) C	H	N	Required (%) C	H	N
Ph	Me	Me	124—126°	*a*	$C_{18}H_{20}N_2$	81·6	8·1	10·4	81·8	7·6	10·6
Ph	Me	CH_2Ph	83—85	*b*	$C_{24}H_{24}N_2$	84·3	7·0	8·1	84·7	7·1	8·2
Ph	–[CH_2]$_5$–		128—130	*a*	$C_{21}H_{24}N_2$	81·9	7·9	8·7	82·9	8·0	9·2
Ph	–[CH_2]$_2$·O·[CH_2]$_2$–		153—156	*a*	$C_{20}H_{22}ON_2$	78·8	7·4	9·3	78·4	7·2	9·1
p-Ph·CH_2O·C_6H_4	Me	Me	142—143	*c*	$C_{25}H_{26}ON_2$	81·4	7·0	7·7	81·0	7·1	7·6
p-HO·C_6H_4	Me	Me	216—217	*d*, *f*	$C_{18}H_{20}ON_2$	76·7	7·5	9·6	77·1	7·2	10·0
p-MeO·C_6H_4	Me	Me	173—175	*c*	$C_{19}H_{22}ON_2$	77·9	7·7	9·5	77·5	7·5	9·5
p-Ph·CH_2·O·C_6H_4	–[CH_2]$_2$·O·[CH_2]$_2$–		159—160	*c*	$C_{27}H_{28}O_2N_2$	78·5	6·7	6·6	78·6	6·8	6·8
p-HO·C_6H_4	–[CH_2]$_2$·O·[CH_2]$_2$–		218—220	*c*	$C_{20}H_{22}O_2N_2$	74·7	6·7	8·6	74·5	6·9	8·7
Ph·CH_2·CH_2	Me	Me	Gum	*g*	—	—	—	—	—	—	—
Ph·CH_2·CH_2	CH_2Ph	CH_2Ph	88—89	*c*	$C_{32}H_{32}N_2$	86·4	7·1	—	86·4	7·3	—
Ph·CH_2·CH_2	H	H	Gum	*h*	$C_{18}H_{20}N_2$	81·4	7·5	—	81·8	7·6	—
p-HO·C_6H_4·CH_2·CH_2	Me	Me	168—169	*i*	$C_{20}H_{24}ON_2$	78·1	7·8	8·4	77·9	7·8	9·1

[a] Ethyl acetate. [b] Benzene–light petroleum (b. p. 60—80°). [c] Methanol. [d] Ethanol. [e] Benzene–acetone. [f] Obtained by debenzylation of the preceding benzyloxy-compound. [g] The *hydrochloride* separated from ether–ethanol; m. p. 162—164° (Found: C, 72·3; H, 7·8; N, 8·2; Cl, 10·8. $C_{20}H_{25}N_2Cl$ requires C, 73·0; H, 7·7; N, 8·5; Cl, 10·8%); *methiodide*, cubes, m. p. 246—248°, from 2-methoxyethanol (Found: C, 58·4; H, 6·4; N, 6·5; I, 29·0. $C_{21}H_{27}N_2I$ requires C, 58·1; H, 6·3; N, 6·5; I, 29·2%). [h] Obtained by debenzylation of the preceding dibenzylamino-compound. [i] Obtained by debenzylation of the oily *O*-benzyl compound which was not isolated.

oxide (3·3 g.) as plates, m. p. 182—184° (Found: C, 73·6; H, 7·2; N, 8·9. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·1; N, 9·0%).

NN-*Diethyl*-α-(1-*methyl*-2-*phenyl*-3-*indolyl*)*lactamide*.—A solution of *NN*-diethyl-1-methyl-2-phenyl-3-indolylglyoxylamide (19 g.) in benzene (300 c.c.) was added very rapidly to methylmagnesium iodide solution [from magnesium (2.2 g.) and methyl iodide (7 c.c.) in ether (50 c.c.)]. Ether was removed by distillation and the clear yellow solution was then refluxed for 2 hr. (bath 110°). After addition of ammonium chloride solution, the separated aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, dried ($MgSO_4$), and evaporated. Trituration of the residual gum with benzene–light petroleum (b. p. 60—80°) gave material, m. p. 126—128° depressed to *ca.* 100° by the starting material. Recrystallisation from benzene–light petroleum (b. p. 80—100°) yielded the *amide* (16·2 g.) as prisms, m. p. 127—129° (Found: C, 75·3; H, 7·7; N, 8·3. $C_{22}H_{26}O_2N_2$ requires C, 75·4; H, 7·5; N, 8·0%).

The following compounds were prepared similarly: NN-*dimethyl*-α-(1-*methyl*-2-*phenyl*-3-*indolyl*)*lactamide*, m. p. 140—142° (from aqueous methanol) (Found: C, 74·9; H, 7·1; N, 8·6. $C_{20}H_{22}O_2N_2$ requires C, 74·5; H, 6·9; N, 8·7%); NN-*diethyl*-α-(1-*methyl*-2-p-*chlorophenyl*-3-*indolyl*)*lactamide*, m. p. 165—166° [from benzene–light petroleum (b. p. 80—100°)] (Found: C, 69·1; H, 6·6; Cl, 9·2. $C_{22}H_{25}O_2N_2Cl$ requires C, 68·7; H, 6·5; Cl, 9·2%). Phenylmagnesium bromide was used similarly to prepare NN-*dimethyl*-(1-*methyl*-2-*phenyl*-3-*indolyl*)*phenylglycollamide* which formed prisms (from methanol), m. p. 156—158° (Found: C, 78·4; H, 6·3; N, 7·4. $C_{25}H_{24}O_2N_2$ requires C, 78·1; H, 6·3; N, 7·3%).

NN-*Diethyl*-N-[2-*hydroxy*-2-(1-*methyl*-2-*phenyl*-3-*indolyl*)*propyl*]*amine*.—Reduction of the foregoing lactic amide by the procedure described above gave the *hydroxy-amine* (75%) as prisms, m. p. 59—60° (from aqueous ethanol) (Found: C, 78·7; H, 8·4; N, 8·5. $C_{22}H_{28}ON_2$ requires C, 78·5; H, 8·4; N, 8·3%).

The following hydroxyamines were prepared similarly: 2-*hydroxy*-2-(1-*methyl*-2-*phenyl*-3-*indolyl*)*propyldimethylamine*, prisms, m. p. 66—67°, from ethanol (Found: C, 78·3; H, 8·3; N, 9·2. $C_{20}H_{24}ON_2$ requires C, 77·9; H, 7·8; N, 9·1%); NN-*diethyl*-2-*hydroxy*-2-(2-p-*chlorophenyl*-1-*methyl*-3-*indolyl*)*propylamine*, prisms, m. p. 92—93°, from aqueous ethanol (Found: C, 71·4; H, 7·4; Cl, 9·6. $C_{22}H_{27}ON_2Cl$ requires C, 71·2; H, 7·3; Cl, 9·6%). β-Hydroxy-β-(1-methyl-2-phenyl-3-indolyl)phenethyldimethylamine, also prepared similarly, was an oil which could not be crystallised. Shaking it with ethyl acetate and 2N-sulphuric acid gave needles of the *hydrogen sulphate hydrate*, m. p. 90° (decomp.) (Found: C, 61·1; H, 6·2; N, 5·5; S, 6·7. $C_{25}H_{26}ON_2,H_2SO_4,H_2O$ requires C, 61·7; H, 6·2; N, 5·8; S, 6·6%).

NN-*Dimethyl*-(1-*methyl*-2-*phenyl*-3-*indolyl*)*glycollamide*.—*NN*-Dimethyl-(1-methyl-2-phenyl-3-indolyl)glyoxylamide (9·7 g.) was suspended in ethanol (200 c.c.) and treated with potassium borohydride (5 g.) in water (50 c.c.); the mixture was warmed at 45—50° for 3 hr., diluted with water (200 c.c.), and acidified with 2N-hydrochloric acid (75 c.c.). Repeated recrystallisation of the solid, which separated on cooling, from ethanol, gave the *hydroxy-amide* as prisms, m. p. 137—139° (Found: C, 74·0; H, 6·9; N, 9·1. $C_{19}H_{20}O_2N_2$ requires C, 74·0; H, 6·5; N, 9·1%.)

3-*Formyl*-1-*methyl*-2-*phenylindole*.—Phosphorus oxychloride (20 c.c.) was added gradually to dimethylformamide (64 c.c.) at 10° and 1-methyl-2-phenylindole (41 g.) in warm dimethylformamide (100 c.c.) was added gradually at 15—20°. The solution was warmed at 35° for 45 min., poured into ice-water (1·5 l.), and stirred until crystallisation occurred (*ca.* 15 min.). 5N-Sodium hydroxide was added until the mixture was neutral to Methyl Red and then more alkali (200 c.c. in all) was added immediately. The mixture was heated to the b. p. and then cooled rapidly. The aldehyde formed plates, m. p. 124—126°, from ethanol (yield, 42 g.); Blume and Lindwall [19] give m. p. 122·5—124°.

1-(1-*Methyl*-2-*phenyl*-3-*indolyl*)-2-*nitroethylene*.—The foregoing aldehyde (7·05 g.) and nitromethane (1·83 g.) were heated with butylamine (0·2 g.) on a steam-bath for 2½ hr. The product, which crystallised on cooling, was triturated with light petroleum (b. p. 60—80°) and recrystallised twice from ethyl acetate to give the *nitro-compound* (4 g.) as prisms, m. p. 149—151° (Found: C, 73·1; H, 5·0; N, 10·5. $C_{17}H_{14}O_2N_2$ requires C, 73·4; H, 5·0; N, 10·1%).

2-(1-*Methyl*-2-*phenyl*-3-*indolyl*)*ethylamine*.—1-(1-Methyl-2-phenylindol-3-yl)-2-nitroethylene (9 g.) in 1,2-dimethoxyethane (500 c.c.) was refluxed for 12 hr. with lithium aluminium hydride (10 g.). Ether (1 l.), ethyl acetate (50 c.c.), and 5N-sodium hydroxide (25 c.c.) were added successively. The mixture was refluxed for 1 hr. and filtered, the solid being washed with

[19] Blume and Lindwall, *J. Org. Chem.*, 1945, **10**, 255.

XUM

ethyl acetate. The amine, obtained by evaporation, did not crystallise but gave the *picrate*, m. p. 215—217°, as prisms from ethanol–acetone (Found: C, 58·0; H, 4·8; N, 14·6. $C_{23}H_{21}O_7N_5$ requires C, 57·6; H, 4·4; N, 14·6%).

In another experiment, the crude amine in ethanol (150 c.c.) was hydrogenated with 40% aqueous formaldehyde (15 c.c.) over 10% palladised charcoal (6 g.). The filtered solution was evaporated and the residual amine treated with ethereal picric acid. Recrystallisation from ethanol gave NN-*dimethyl*-2-(1-*methyl*-2-*phenyl*-3-*indolyl*)*ethylamine picrate* (7·0 g.) as prismatic needles, m. p. 152—154° (Found: C, 59·5; H, 5·4; N, 13·7. $C_{25}H_{25}O_7N_5$ requires C, 59·2; H, 5·0; N, 13·8%). The *amine*, liberated from the picrate by sodium hydroxide solution and isolated with ether, was a yellow syrup (Found: C, 81·4; H, 8·0; N, 9·9. $C_{19}H_{22}N_2$ requires C, 82·0; H, 8·0; N, 10·1%).

NN-*Di*-(2-*hydroxyethyl*)-2-(1-*methyl*-2-*phenyl*-3-*indolyl*)*ethylamine*.—Another portion (10 g.) of the foregoing nitro-compound was reduced similarly and the crude amine was dissolved in methanol (100 c.c.). Ethylene oxide (40 g.) was slowly bubbled through the solution which was then left overnight. Evaporation furnished a gum which was converted into the *picrate*, m. p. 160—163° (Found: C, 57·1; H, 5·2; N, 12·3. $C_{27}H_{29}O_9N_5$ requires C, 57·1; H, 5·2; N, 12·3%). The *dihydroxy-amine*, liberated as in the previous example, crystallised from ethanol and had m. p. 91—92° (Found: C, 74·6; H, 7·5; N, 8·3. $C_{21}H_{26}O_2N_2$ requires C, 74·5; H, 7·7; N, 8·3%).

Ethyl α-*Cyano*-β-(1-*methyl*-2-*phenyl*-3-*indolyl*)*acrylate*.—A mixture of 3-formyl-1-methyl-2-phenylindole (18 g.), pyridine (22·5 c.c.), piperidine (3·25 c.c.), ethyl cyanoacetate (11·25 c.c.), and propan-2-ol (45 c.c.) was refluxed for 20 min. (cf. Blume and Lindwall [7]). When ethanol–water (100 c.c.; 7 : 3) was added to the cooled mixture, yellow needles separated. Recrystallisation from ethanol gave the *ester* (21 g.), m. p. 142° (Found: C, 76·5; H, 5·3; N, 8·4. $C_{21}H_{18}O_2N_2$ requires C, 76·3; H, 5·4; N, 8·5%).

(1-*Methyl*-2-*phenyl*-3-*indolylmethyl*)*malonic Acid*.—The foregoing ester (5·0 g.) in ethanol (60 c.c.) was hydrogenated in the presence of 10% palladised charcoal (0·5 g.) and 10% palladised strontium carbonate (0·5 g.) until 400 c.c. of hydrogen had been absorbed. Evaporation of the filtered solution gave a glass which was refluxed for 80 hr. with potassium hydroxide (3·5 g.) in water (50 c.c.) and ethanol (50 c.c.). The filtered solution was acidified and extracted with ethyl acetate, and the extracts were washed with water and dried (Na_2SO_4). On trituration of the oily residue with ethylene dichloride it crystallised, and recrystallisation of the solid from aqueous ethanol furnished the *diacid* (2·75 g.) as prisms, m. p. 172° (Found: C, 71·1; H, 5·5; N, 4·5. $C_{19}H_{17}O_4N$ requires C, 70·6; H, 5·3; N, 4·3%).

β-(1-*Methyl*-2-*phenyl*-3-*indolyl*)*propionic Acid*.—After the diacid (2·8 g.) had been heated at 180° until decarboxylation ceased (2·5 hr.), the residual gum was triturated with aqueous ethanol to give the acid which was recrystallised from aqueous ethanol and then from light petroleum (b. p. 80—100°). It formed prisms (2·25 g.), m. p. 106—108° (Found: C, 77·1; H, 6·2; N, 5·0. Calc. for $C_{18}H_{17}O_2N$: C, 77·4; H, 6·1; N, 5·0%). Harley-Mason [20] gave m. p. 114—116°.

A suspension of the acid (3·8 g.) in benzene (75 c.c.) was stirred with oxalyl chloride (5 g.) for 3·5 hr., and excess of dimethylamine was passed into the resulting solution. The mixture was washed with water and evaporated, the resulting *dimethylamide* (3·5 g.), m. p. 99—100°, being isolated by recrystallisation from benzene–light petroleum (b. p. 60—80°) (Found: C, 78·1; H, 7·0; N, 9·4. $C_{20}H_{22}ON_2$ requires C, 78·4; H, 7·2; N, 9·1%).

NN-*Dimethyl*-3-(1-*methyl*-2-*phenyl*-3-*indolyl*)*propylamine*.—Reduction of the dimethylamide (3·3 g.) with lithium aluminium hydride (3 g.) in ether–benzene according to the general procedure yielded the *amine* (1·65 g.), prisms, m. p. 47—49° [from light petroleum (b. p. 40—60°)] (Found: C, 81·8; H, 8·3; N, 9·4. $C_{20}H_{24}N_2$ requires C, 82·1; H, 8·3; N, 9·6%).

3-*Cyano*-1-*methyl*-2-*phenylindole*.—3-Formyl-1-methyl-2-phenylindole oxime [19] (5·0 g.) and acetic anhydride (50 c.c.) were heated under reflux for 2 hr. and then evaporated *in vacuo*. The solid residue was recrystallised from ethanol to give 3-*cyano*-1-*methyl*-2-*phenylindole* (2 g.) as needles, m. p. 117—119° (Found: C, 82·7; H, 5·1; N, 12·3. $C_{16}H_{12}N_2$ requires C, 82·7; H, 5·2; N, 12·1%).

1-*Methyl*-2-*phenylindole*-3-*carboxylic Acid*.—The cyano-indole (7 g.) and potassium hydroxide (20 g.) in water (20 c.c.) and ethylene glycol (100 c.c.) were refluxed together for 72 hr. Water (100 c.c.) was added and the hot solution was filtered and acidified with acetic acid (50 c.c.).

[20] Harley-Mason, *J.*, 1952, 2433.

The acid was collected and recrystallised from benzene to give tablets (5·2 g.), m. p. 200—201°. Borsche and Klein [21] report m. p. 201—202°.

3-Dimethylaminoacetyl-2-phenylindole.—Ethylmagnesium iodide solution (from 4·5 g. of magnesium) in ether (100 c.c.) was stirred and cooled (ice-bath) while 2-phenylindole (26 g.) in ether (300 c.c.) was added rapidly. After 5 min. chloroacetyl chloride (20 g.) in ether (50 c.c.) was added. The mixture was stirred and cooled for 15 min., then treated with ammonium chloride solution and extracted with benzene. The combined organic layers were washed with water, sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and concentrated to small volume. 2-Phenylindole, which gradually separated, was filtered off; evaporation of the filtrate gave a gum which was refluxed (bath 120°) with 2-methoxyethanol (50 c.c.) and 30% ethanolic dimethylamine (50 c.c.) for 5 hr. The residue obtained by evaporation under reduced pressure was dissolved in ethyl acetate, washed with sodium carbonate solution and water, and extracted with 2N-sulphuric acid (2 × 75 c.c.). Basification of the acid extracts followed by isolation with ethyl acetate and evaporation yielded a gum which crystallised on trituration with a little ethyl acetate. Recrystallisation from ethyl acetate gave prisms of the *keto-amine*, m. p. 188—190° (Found: C, 77·5; H, 6·3; N, 9·8. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 6·5; N, 10·1%).

Reduction of N,N,2-Triphenyl-3-indolylglyoxylamide by Lithium Aluminium Hydride.—The *amide* was prepared by the general procedure except that diphenylamine (50 g.) in pyridine (150 c.c.) was added to the acid chloride from 2-phenylindole (35 g.). It formed cream-coloured needles, m. p. 263—265°, from 2-methoxyethanol (Found: C, 81·0; H, 5·0; N, 6·5. $C_{28}H_{20}O_2N_2$ requires C, 80·7; H, 4·8; N, 6·7%).

Reduction of the amide (8 g.) with lithium aluminium hydride (5 g.) in 1,2-dimethoxyethane was carried out according to the general procedure. The resulting gum was refluxed for 8 hr. with acetic anhydride and then distilled to give the product, b. p. 180—200°/0·2 mm. Redistillation gave *3-(2-acetoxyethyl)-2-phenylindole*, b. p. 180—184°/0·2 mm., n_D^{20} 1·6374 (Found: C, 77·6; H, 6·2; N, 5·4. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1; N, 5·0%).

1-Methyl-2-phenyl-3-indolylacetonitrile.—A mixture of acetic acid (70 c.c.), diethylamine (6·0 g.), 40% formaldehyde solution (5·9 c.c.), and 1-methyl-2-phenylindole (16·1 g.) was stirred and cooled in ice-water for 6 hr. Water (1 l.) was added and the filtered solution was basified with aqueous ammonia and extracted with ether–ethyl acetate (1 : 1), the extracts being washed with water, dried (Na_2SO_4), and evaporated *in vacuo* (bath 40°). The residue was taken up in ethanol (100 c.c.), ether (50 c.c.) and methyl iodide (10 c.c.) and left overnight. *NN-Diethyl-(1-methyl-2-phenyl-3-indolylmethyl)amine methiodide* (21 g.) was collected and washed with ether; it decomposed at *ca.* 150° (Found: C, 58·4; H, 6·5; N, 6·2; I, 28·9. $C_{21}H_{27}N_2I$ requires C, 58·1; H, 6·3; N, 6·5; I, 29·2%). When dimethylamine was used similarly in place of diethylamine, a large amount of precipitate was obtained on addition of water to the reaction mixture. Recrystallisation from butan-2-one gave *di-(1-methyl-2-phenyl-3-indolyl)methane*, plates, m. p. 177—179° (Found: C, 87·3; H, 6·1; N, 7·2. $C_{31}H_{26}N_2$ requires C, 87·3; H, 6·1; N, 6·6%).

The foregoing methiodide (21 g.), sodium cyanide (11 g.), and dimethylformamide (100 c.c.) were refluxed for 20 hr. (cf. Woodward *et al.*[11]). Water (800 c.c.) was added and the oily product was isolated with ethyl acetate. Evaporation furnished the *nitrile* (10·9 g.), which formed prisms, m. p. 101—102°, from methanol (Found: C, 82·5; H, 6·0; N, 11·6. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7; N, 11·4%).

1-Methyl-2-phenyl-3-indolylacetic Acid.—The crude nitrile (from methiodide, 14 g.) was refluxed with 2-methoxyethanol (50 c.c.) and potassium hydroxide (20 g.) in water (50 c.c.) for 20 hr. After addition of water (100 c.c.), the hot solution was filtered to remove some gum and poured into ice-cold dilute hydrochloric acid. The *acid* which separated was recrystallised from benzene–light petroleum (b. p. 60—80°) to give prisms (7·2 g.), m. p. 147—149° (Found: C, 77·3; H, 5·7; N, 5·5. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7; N, 5·3%).

The derived *N-methylamide* (obtained by successive treatment with oxalyl chloride in ether and dimethylamine) formed plates, m. p. 177—179°, from ethanol (Found: C, 77·7; H, 6·9; N, 10·0. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 6·5; N, 10·1%).

2-(1-Methyl-2-phenyl-3-indolyl)-1-phenylethylamine Picrate.—A solution of phenylmagnesium bromide [from bromobenzene (9·4 g.) and magnesium (1·3 g.) in ether (100 c.c.)] was refluxed while 1-methyl-2-phenyl-3-indolylacetonitrile (10·5 g.) was added rapidly. After the mixture had been refluxed for 1 hr., a slurry of lithium aluminium hydride (5 g.) in ether

XUM

(400 c.c.) was added. The mixture was refluxed for 3 hr., then worked up by the general procedure, but the gummy product did not crystallise. It was taken up in ether (100 c.c.) and added to picric acid (12 g.) in ether (1 l.). The precipitated oil which gradually crystallised was recrystallised from methanol to give the *picrate* (10·5 g.) as dark red needles, m. p. 198—199° (decomp.) (Found: C, 62·2; H, 5·1; N, 12·1. $C_{29}H_{25}O_5N_7$ requires C, 62·7; H, 4·5; N, 12·6%).

NN-*Dimethyl*-2-(1-*methyl*-2-*phenyl*-3-*indolyl*)-1-*phenylethylamine*.—The foregoing picrate (10 g.) was shaken with 0·5N-sodium hydroxide (1 l.) and ether (500 c.c.) until all the solid had been decomposed. The organic layer was washed with 0·5N-sodium hydroxide (2 × 50 c.c.) and water (2 × 50 c.c.), dried (Na_2SO_4), and evaporated; the residual amine was hydrogenated with 40% aqueous formaldehyde (10 c.c.) in ethanol (70 c.c.) in the presence of 10% palladised charcoal (3 g.) until absorption ceased. Evaporation of the filtered solution gave a gum which was dissolved in ether and stirred with 2N-sulphuric acid (200 c.c.). The colourless plates of hydrated *amine hydrogen sulphate* (4·5 g.) were collected, washed with ether and 2N-sulphuric acid, and dried *in vacuo* at room temperature; the salt decomposed rapidly above 120° and darkened slowly at room temperature (Found: C, 62·1; H, 6·2; N, 5·7; S, 7·0. $C_{25}H_{26}N_2,H_2SO_4,2H_2O$ requires C, 61·5; H, 6·6; N, 5·7; S, 6·6%).

A portion of the salt (1·5 g.) was decomposed with sodium hydroxide solution, and the amine was isolated by means of ethyl acetate, and treated with ethereal picric acid. Deep red crystals, m. p. 130° (decomp.), of the *dipicrate* slowly separated (Found: C, 54·8; H, 4·4; N, 13·7. $C_{37}H_{32}O_{14}N_8$ requires C, 54·7; H, 4·0; N, 13·8%).

NN-*Dimethyl*-β-(2-*phenyl*-3-*indolyl*)*phenethylamine*.—2-Nitro-1-phenyl-1-(2-phenyl-3-indolyl)-ethane [12] (5 g.) in ethanol (70 c.c.) was hydrogenated with 10% palladised charcoal until absorption ceased; 36% aqueous formaldehyde (10 c.c.) and 10% palladised charcoal (2 g.) were added and hydrogenation was resumed until absorption ceased. Evaporation of the filtered solution gave NN-*dimethyl*-β-(2-*phenyl*-3-*indolyl*)*phenethylamine* (3·3 g.), prisms, m. p. 180—182°, from ethanol (Found: C, 84·3; H, 6·9; N, 8·3. $C_{24}H_{24}N_2$ requires C, 84·6; H, 7·1; N, 8·2%).

β-(2-*Phenyl*-3-*indolyl*)*phenethylurea*.—The foregoing primary amine (4 g.) was boiled with 0·15N-hydrochloric acid (85 c.c.); the solution was cooled and filtered and treated with potassium cyanate (1 g.). After 1·5 hr., the precipitate was collected and boiled with water (200 c.c.); decantation of the aqueous solution left an oil which crystallised on trituration with ethanol. Recrystallisation from ethanol afforded the *urea* (1·4 g.) as needles, m. p. 153—155° (Found: C, 77·2; H, 6·4; N, 11·6. $C_{23}H_{21}ON_3$ requires C, 77·7; H, 6·0; N, 11·8%).

N-*Ethoxycarbonyl*-β-(2-*phenyl*-3-*indolyl*)*phenethylamine*.—Ethyl chloroformate (0·9 c.c.) was added to an ice-cold solution of β-(2-phenyl-3-indolyl)phenethylamine (3 g.) in pyridine (50 c.c.) and the mixture was left overnight. After addition of water (200 c.c.), the *urethane* (1·5 g.) was isolated with ether; recrystallised from ethanol, it had m. p. 138—139° (Found: C, 76·3; H, 6·7; N, 7·1. $C_{25}H_{24}O_2N_2,0·5H_2O$ requires C, 76·4; H, 6·3; N, 7·1%).

NN-*Di*-(2-*hydroxyethyl*)-β-(2-*phenyl*-3-*indolyl*)*phenethylamine*.—Ethylene oxide was bubbled through a solution of the indolylethylamine (5 g.) in methanol (200 c.c.) for 2 hr. The solution was left at room temperature for 20 hr., then concentrated to small volume. The *amine* (2·7 g.) which separated on cooling recrystallised from methanol as prisms, m. p. 178—179° (Found: C, 78·4; H, 7·5; N, 7·4. $C_{26}H_{28}O_2N_2$ requires C, 78·0; H, 7·1; N, 7·0%).

2-*Nitro*-1-*phenyl*-1-(2-p-*chlorophenyl*-3-*indolyl*)*ethane*.—A mixture of 2-*p*-chlorophenylindole (50 g.), β-nitrostyrene (40 g.), and 2-butoxyethanol (500 c.c.) was refluxed for 14 hr. and then evaporated under reduced pressure. Recrystallisation of the residue from ethanol gave the *nitro-compound* (51 g.), m. p. 164—165° (Found: C, 70·3; H, 5·0; N, 7·2. $C_{22}H_{17}O_2N_2Cl$ requires C, 70·1; H, 4·6; N, 7·4%). When the solvent was omitted a much lower yield was obtained.

β-(2-p-*Chlorophenyl*-3-*indolyl*)*phenethylamine*.—The foregoing nitro-compound (8 g.) in methanol (100 c.c.) was hydrogenated in the presence of 1 g. of platinised charcoal.[22] After an induction period of about 1 hr., hydrogenation proceeded slowly and was complete in 30 hr. The filtered solution was evaporated and the residue recrystallised from ethanol to give the *amine* (2 g.), m. p. 182—184° (Found: C, 76·1; H, 5·9; N, 8·1. $C_{22}H_{19}N_2Cl$ requires C, 76·2; H, 5·5; N, 8·1%).

[21] Borsche and Klein, *Annalen*, 1941, **584**, 64.
[22] Baltzly, *J. Amer. Chem. Soc.*, 1952, **74**, 4586.

β-p-*Chlorophenyl*-β-(2-*phenyl*-3-*indolyl*)*phenethylamine*.—2-Phenylindole (20 g.) and 4-chloro-nitrostyrene [23] (19 g.) were fused together (bath 130°) for 6 hr. A solution of the mass in hot ethanol was filtered (charcoal) and cooled to give 1-p-*chlorophenyl*-2-*nitro*-1-(2-*phenyl*-3-*indolyl*)-*ethane* (27 g.) which formed yellow prisms, m. p. 147—148°, on recrystallisation from ethanol (Found: C, 69·7; H, 4·8; N, 7·7%).

Hydrogenation of the nitro-compound (10 g.) in the presence of platinised charcoal as in the previous example gave the *amine* (4·4 g.) as needles, m. p. 188—190° (Found: C, 76·2; H, 5·4; N, 7·7%).

N-*Benzoyl*-β-3-*indolylphenethylamine*.—Benzoylation (benzoyl chloride–pyridine overnight at room temperature) of β-3-indolylphenethylamine [12] gave the *benzoyl derivative*, needles, m. p. 188° (from ethanol) (Found: C, 80·4; H, 5·8; N, 8·0. $C_{23}H_{20}ON_2$ requires C, 81·1; H, 5·9; N, 8·2%).

N-*Benzoyl*-N-*methyl*-β-(1-*methyl*-3-*indolyl*)*phenethylamine*.—The foregoing benzoyl derivative (8·5 g.) was added to a solution of sodamide (from sodium, 3 g.) in liquid ammonia (250 c.c.). After 45 min., methyl iodide (9 c.c.) was added and the solvent was allowed to evaporate. The solid obtained on addition of water (200 c.c.) recrystallised from ethanol to give needles of the *amide*, m. p. 139—141° (Found: C, 81·8; H, 6·5; N, 7·7; *N*-Me, 9·9. $C_{25}H_{24}ON_2$ requires C, 81·5; H, 6·6; N, 7·6; *N*-Me, 8·2%).

N-*Methyl*-β-(1-*methyl*-3-*indolyl*)*phenethylamine*.—Reduction of the amide (6·2 g.) with lithium aluminium hydride (5 g.) in ether (150 c.c.) and benzene (150 c.c.) by the general procedure furnished the *N*-benzylamine as a yellow oil. A small portion was catalytically hydrogenated and then treated with ethereal picric acid, to give the *amine picrate*, dark red prisms, m. p. 181° (from ethanol) (Found: C, 57·9; H, 4·8; N, 13·9. $C_{24}H_{23}O_7N_5$ requires C, 58·4; H, 4·7 N, 14·2%).

NN-*Dimethyl*-β-(1-*methyl*-3-*indolyl*)*phenethylamine*.—The foregoing crude benzylamine (1·9 g.) in ethanol (50 c.c.) was hydrogenated in the presence of 10% palladised charcoal (0·5 g.). When 1 mol. of hydrogen had been absorbed (3·5 hr.), 40% aqueous formaldehyde (0·9 c.c.) and more catalyst (1 g.) were added and hydrogenation was resumed until absorption ceased. Evaporation of the filtered solution gave an oil which with ethereal citric acid gave the *amine citrate dihydrate* (1·45 g.) as prisms, m. p. 69° (decomp.) (Found: C, 59·7; H, 7·1; N, 5·1; *N*-Me, 8·3. $C_{25}H_{30}O_7N_2,2H_2O$ requires C, 59·3; H, 6·8; N, 5·5; *N*-Me, 8·9%).

In another experiment, the crude amine was treated with ethereal picric acid to give the orange *picrate*, m. p. 199° (Found: C, 58·8; H, 5·3; N, 13·4. $C_{25}H_{25}O_7N_5$ requires C, 59·2; H, 5·0; N, 13·8%).

2-*Formyl*-1,2,3,4-*tetrahydro*-4-*phenyl*-β-*carboline*.—β-3-Indolylphenethylamine (4·7 g.), 40% formaldehyde (1·8 c.c.), and water (4 c.c.) were added successively to 90% formic acid (2·6 c.c.) in ice-water. The mixture was refluxed for 16 hr., poured into N-sodium hydroxide, and extracted repeatedly with benzene. A solid, which separated on concentration of the extracts to small volume, recrystallised from benzene–cyclohexane to give the *amide* (2·0 g.), prisms, m. p. 235—236° (Found: C, 78·7; H, 5·9; N, 9·8. $C_{18}H_{16}ON_2$ requires C, 78·2; H, 5·8; N, 10·1%).

1,2,3,4-*Tetrahydro*-2-*methyl*-4-*phenyl*-β-*carboline*.—The foregoing amide (2 g.) was reduced with lithium aluminium hydride (2 g.) in ether–benzene according to the general procedure. The resulting *amine* separated from benzene as needles (1·5 g.), m. p. 216—218° (Found: C, 82·2; H, 7·1; N, 10·1; *N*-Me, 4·8. $C_{18}H_{18}N_2$ requires C, 82·4; H, 6·9; N, 10·7; *N*-Me, 5·7%).

N-*Benzoyl*-β-(2-*phenyl*-3-*indolyl*)*phenethylamine*.—β-(2-Phenyl-3-indolyl)phenethylamine (11·2 g.) was benzoylated (benzoyl chloride–pyridine at room temperature) to give the *amide* (7·5 g.) as prisms, m. p. 188—189° (from ethanol) (Found: C, 83·7; H, 5·5; N, 6·9. $C_{29}H_{24}ON_2$ requires C, 83·6; H, 5·8; N, 6·7%).

N-*Benzoyl*-N-*methyl*-β-(1-*methyl*-2-*phenyl*-3-*indolyl*)*phenethylamine*.—The foregoing amide (2 g.) and methyl iodide (3·4 g.) were added successively to sodamide (from sodium, 0·5 g.) in liquid ammonia (40 c.c.). After the ammonia had evaporated, the residue was washed with water and recrystallised from ethanol to furnish the *product* (1·0 g.), needles, m. p. 168—169° (Found: C, 83·8; H, 6·4; N, 6·2; *N*-Me, 5·8. $C_{31}H_{28}ON_2$ requires C, 83·8; H, 6·4; N, 6·3; *N*-Me, 6·8%).

N-*Benzyl*-N-*methyl*-β-(1-*methyl*-2-*phenyl*-3-*indolyl*)*phenethylamine*.—The methylation product (14 g.) was reduced with lithium aluminium hydride (10 g.) in ether–benzene (each 300 c.c.) by

[23] Campbell, Anderson, and Gilmore, *J.*, 1940, 446.

XUM

the general procedure. The *amine* (8·5 g.) separated from ethanol as prisms, m. p. 83—85° (Found: C, 86·2; H, 7·1; N, 6·5; *N*-Me, 7·1. $C_{31}H_{30}N_2$ requires C, 86·5; H, 7·0; N, 6·5; *N*-Me, 7·0%). It gave the *picrate* as orange prisms, m. p. 148—150° (Found: C, 67·5; H, 5·1; N, 10·5. $C_{37}H_{33}O_7N_5$ requires C, 67·4; H, 5·0; N, 10·6%).

NN-*Dimethyl*-β-(1-*methyl*-2-*phenyl*-3-*indolyl*)*phenethylamine*.—A suspension of the foregoing benzylamine (2·5 g.) in ethanol (50 c.c.) was hydrogenated in the presence of 10% palladised charcoal (0·5 g.) and 10% palladised strontium carbonate (0·5 g.). After hydrogen (1 mol.) had been absorbed in 6 hr., 40% aqueous formaldehyde (0·9 c.c.) and more palladised charcoal (1 g.) were added and hydrogenation was continued until absorption ceased. Evaporation of the filtered solution afforded the *amine* (1·3 g.), prisms, m. p. 122—124° (from ethanol) (Found: C, 84·5; H, 7·2; N, 7·9. $C_{25}H_{26}N_2$ requires C, 84·7; H, 7·4; N, 7·9%).

4-(1-*Methyl*-2-*phenyl*-3-*indolylmethylene*)-2-*phenyloxazol*-5-*one*.—Hippuric acid (3·6 g.), anhydrous sodium acetate (1·64 g.), and 3-formyl-1-methyl-2-phenylindole (4·7 g.) were ground together and then treated with acetic anhydride (10 c.c.); the mixture was heated on a steam-bath for 20 min., cooled, and shaken with water (50 c.c.). The solid was collected and recrystallised from acetic acid (charcoal) and then from 2-methoxyethanol to give the *oxazolone* (2·7 g.), yellow plates, m. p. 240—242° (Found: C, 79·2; H, 5·0; N, 7·1. $C_{25}H_{18}O_2N_2$ requires C, 79·4; H, 4·8; N, 7·4%).

1-*Methyl*-2-*phenyltryptophan*.—Sodium (1·5 g.) was dissolved in dry ethanol (50 c.c.), and the solution evaporated to small volume; a foam of sodium ethoxide was then obtained by sudden reduction of pressure. After the foam had been dried *in vacuo* for 5 min., dioxan (150 c.c.; redistilled from sodium) and ethyl acetamidomalonate (13·4 g.) were added successively. The mixture was refluxed (bath 140°) for 1·5 hr. and cooled; *NN*-diethyl-(1-methyl-2-phenyl-3-indolylmethyl)amine methiodide (28 g.; finely powdered) was added and the mixture was refluxed (bath 120°) for 30 hr., then poured into water (500 c.c.). The oily product was isolated with ether and hydrolysed for 3 hr. with potassium hydroxide (30 g.) in boiling ethanol (100 c.c.) and water (100 c.c.) (bath 130°). After addition of water (100 c.c.), ethanol was removed by distillation; the cooled solution was filtered and treated with excess of ice and then concentrated hydrochloric acid (50 c.c.). The precipitate was boiled with water (200 c.c.) for 2·5 hr.; N-*acetyl*-1-*methyl*-2-*phenyltryptophan* (15 g.) was collected by filtration of the cooled mixture and was recrystallised from ethanol; it formed needles, m. p. 230—232° (decomp.) (Found: C, 71·8; H, 6·2; N, 8·2. $C_{20}H_{20}O_3N_2$ requires C, 71·4; H, 6·0; N, 8·3%).

A solution of the acetamido-acid (14 g.) in 3N-potassium hydroxide was refluxed for 24 hr., cooled, and acidified with acetic acid. The precipitate was collected and recrystallised from aqueous ethanol, to give 1-*methyl*-2-*phenyltryptophan*, m. p. 200—202° (decomp.) (Found: C, 73·0; H, 6·3; N, 9·3. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·2; N, 9·5%)

The authors are indebted to Dr. R. E. Bowman for helpful discussions, to Mr. F. H. Oliver for microanalyses, and to Miss E. M. Tanner for spectroscopic measurements.

RESEARCH DEPARTMENT, PARKE, DAVIS & CO. LTD.,
HOUNSLOW, MIDDLESEX.

[*Received, May 1st*, 1959.]

686. *The Barium Fluoride–Uranium Tetrafluoride and the Strontium Fluoride–Thorium Tetrafluoride System.*

By R. W. M. D'Eye and I. F. Ferguson.

The BaF_2–UF_4 and the SrF_2–ThF_4 system have been examined by *X*-ray diffraction and density measurements. The tetrafluoride dissolves in the difluoride to the extent of about 25 moles %, the unit-cell constant decreasing in the former and increasing in the latter system. Barium and strontium fluorides dissolve in barium uranium hexafluoride and strontium thorium hexafluoride respectively to the extent of about 20 moles % with the creation of anion vacancies. At 60 moles % of uranium tetrafluoride a previously unidentified compound is formed. Below this exists a two-phase region down to UF_4. An analogous compound is not found in the SrF_2–ThF_4 system, so that, between 50 and 100 moles % of thorium tetrafluoride, only strontium thorium hexafluoride and thorium tetrafluoride are found.

From *X*-ray diffraction and density studies of anomalous mixed crystal systems such as CaF_2–YF_3,[1,2,3] CaF_2–ThF_4,[3] BaF_2–UF_3,[4] and ThO_2–ThF_4,[5] it has been concluded that the fluorite mixed-crystal phase contains interstitial anions and that, at the solid-solubility limit, the fluorite unit cell contains two additional fluorine atoms. Further, the unit cell contracts when the substituting cation is smaller and has a higher charge and expands when it is of similar size. These conclusions are substantiated by the present work.

Barium uranium hexafluoride, strontium thorium hexafluoride, and thorium oxide difluoride are reported [6] to have the LaF_3-type hexagonal structure with a random distribution of cations in the first two and of anions in the last compound. Although later work showed that the true symmetry of thorium oxide fluoride was lower than this, presumably because of the distortion brought about by an ordering of the anions,[5] no similar evidence is found in the present work to suggest a lower symmetry, and hence an ordering of the cations, for the two hexafluorides.

Barium and strontium fluoride dissolve in barium uranium hexafluoride and strontium thorium hexafluoride respectively with the formation of anion vacancies rather than interstitial cations. In both instances the solid solubility limit is about 20 moles %. Thus the mode of incorporation of the difluoride into the lattice is strictly analogous to that of barium fluoride into uranium trifluoride.[4]

Experimental

Materials.—"AnalaR" strontium fluoride was used. Barium fluoride was precipitated by ammonium fluoride from a barium nitrate solution. Uranium tetrafluoride was prepared by hydrofluorination of uranium dioxide, and thorium tetrafluoride by dehydration of a hydrate, ThF_4,yH_2O.[7]

Mixed Crystals.—The requisite amounts of the constituents were intimately mixed and heated for about 30 min. in graphite crucibles in an atmosphere of argon. This was first purified by passing it through traps cooled with liquid oxygen and then over heated, freshly reduced, copper turnings. Samples rich in barium fluoride and uranium tetrafluoride were heated at 1200° c and 900° c respectively, and those rich in strontium fluoride and thorium tetrafluoride were heated at 1350° and 1000° respectively. To ensure that the mixed crystals were homogeneous they were ground and re-heated. Mixtures of approximately equimolar proportions were cooled slowly, by gradually lowering the temperature of the furnace, and quickly, by

[1] Vogt, *Neues Jahrb. Min.*, 1914, **2**, 9.
[2] Goldschmidt, *Geochem. Verteilungsgesetze*, 1926, **7**, 88.
[3] Zintl and Udgård, *Z. anorg. Chem.*, 1939, **240**, 150.
[4] D'Eye and Martin, *J.*, 1957, 1847.
[5] D'Eye, *J.*, 1958, 196.
[6] Zachariasen, *Acta Cryst.*, 1949, **2**, 388.
[7] D'Eye and Booth, *J. Inorg. Nuclear Chem.*, 1955, **1**, 326; 1957, **4**, 13; D'Eye, Booth, and Harper, U.K.A.E.A. Report A.E.R.E. C/R 1735 (1955).

XUM

immediate removal from the furnace. Although graphite crucibles were used no evidence of carbide formation was observed.

X-Ray Diffraction Analysis.—Photographs were obtained with a Guinier-type focusing camera,[8] monochromatised and focused Cu-K_α radiation from a bent quartz plate being used. A 0·1 mm. scale was photographed on the film before processing, to avoid shrinkage errors in the measurement of the Bragg angle.

Pyknometric Density.—Densities were calculated from the difference in weight of the material in air and in toluene. Low values, caused by incomplete filling of the microcapillaries in the surface structure of the crystals, were avoided by adding the pyknometric liquid to the solid under a vacuum. Both the solid and the toluene were outgassed before use.

Chemical Analysis.—The fluorine in the sample was estimated by the pyrohydrolytic method.[9] Steam was passed over the sample in a platinum boat, which was heated to 900—1000°. The resulting hydrofluoric acid–water mixture was condensed and titrated with standard alkali. The steam-jet was then removed, and the residual oxide ignited in air and weighed.

Results and Discussion

The cell constant of the BaF_2–UF_4 fluorite mixed-crystal phase decreases approximately linearly with increasing uranium tetrafluoride content down to the solid solubility limit of about 25 moles % (Table 1). From the cell constant the density was calculated on the basis of: (i) interstitial anions with a complete cation lattice, and (ii) a complete anion lattice with a defective cation lattice. The measured density corresponds closely to that calculated on the former assumption (Table 1).

Table 1.

BaF_2–UF_4 *anomalous mixed crystals*

UF_4 (moles %)	$a \pm 0{\cdot}005$ (Å)	d, calc. on interstitial anions (g./c.c.)	d, calc. on vacant cations (g./c.c.)	d, measured (g./c.c.)
0	6·198		4·88	4·85
10	6·152	5·41	4·91	5·31
15	6·144	—	—	—
20	6·122	5·87	4·89	5·81
25	6·097	—	—	—
30	6·098		plus hexagonal phase.	

SrF_2–ThF_4 *anomalous mixed crystals*

ThF_4 (moles %)	$a \pm 0{\cdot}005$ (Å)	
0	5·808	
10	5·817	
20	5·837	
26	5·839	
28	5·848	plus hexagonal phase
32	5·851	plus hexagonal phase

At the limit of solid solubility of uranium trifluoride in barium fluoride, 50 moles %, the unit cell has a parameter of 6·046 Å and contains ten F^-, two U^{3+}, and two Ba^{2+} ions, the cations being randomly distributed over the normal cation positions.[4] In the present system at the solid solubility limit the unit cell has a parameter of 6·097 Å, again contains ten F^- ions, but now the cation lattice comprises a random distribution of one U^{4+} and three Ba^{2+} ions. The cell parameter, as might be expected, is greater in this instance because only one Ba^{2+} ion has been replaced by a smaller, more highly charged ion.

The cell constant of the SrF_2–ThF_4 mixed crystals increases, in contrast to the previous system, with increasing tetrafluoride content up to the solid solubility limit at about 25 moles % (Table 1). The difference between the ionic radii of Sr^{2+} (1·13 Å) and Th^{4+}

[8] D'Eye, U.K.A.E.A. Report A.E.R.E. C/R 1524 (1954).
[9] Gillies, Keen, Lister, and Rees, U.K.A.E.A. Report A.E.R.E. C/M 225 (1954).

(0·95 Å) is less than that between Ba^{2+} (1·35 Å) and U^{4+} (0·89 Å) and is apparently insufficient to compensate for the distortion effect of the interstitial anions. Thus the lattice expands with increasing interstitial content.

Between about 75 and 56 moles % of difluoride, the diffraction photographs show that two phases are present: a fluorite phase representing the limit of solid solubility of the tetrafluoride in the difluoride, and a hexagonal phase representing the limit of solid solubility of the difluoride in the MXF_6 (M = Ba, Sr; X = U, Th) compound.

The incorporation of the difluoride into the compound MXF_6 must lead to either vacant anion sites or interstitial cations. A comparison between the densities calculated on these two assumptions with that observed shows the former to be correct (Table 2).

TABLE 2.

$BaUF_6$–BaF_2 *anomalous mixed crystals*						$SrThF_6$–SrF_2 *anomalous mixed crystals*		
BaF_2 (moles %)	$a \pm 0.005$ (Å)	$c \pm 0.005$ (Å)	*d*, calc. on vacant anions (g./c.c.)	*d*, calc. on interstitial cations (g./c.c.)	*d*, measured (g./c.c.)	SrF_2 (moles %)	$a \pm 0.005$ (Å)	$c \pm 0.005$ (Å)
0	4·279	7·481		6·85	6·76	0	4·132	7·341
11	4·286	7·493	6·70	6·85	6·67	8	4·136	7·365
15	4·283	7·492	6·67	6·86	6·64	15	4·138	7·368
21	4·281	7·504	6·59	6·87	6·56			
28	4·282	7·506		plus cubic phase				

When barium fluoride dissolves in uranium trifluoride,[4] which is isostructural with $BaUF_6$ and $SrThF_6$, both the *a* and the *c* axis expand. However, in the present work it can be seen from Table 2 that only the *c* axis expands appreciably. This still does not allow a prediction to be made whether the anion vacancies are randomly distributed or concentrated in one or other of the two structurally different sets of anion positions.[4,5]

The observed and calculated values of $\sin^2\theta$ for barium uranium hexafluoride, indexed on the basis of a hexagonal LaF_3-type structure, are given in Table 3. The diffraction patterns of this salt and of strontium thorium hexafluoride were the same irrespective of the rate at which the materials were cooled. It was therefore impossible to prepare these compounds with an ordered arrangement of the cations.

TABLE 3. *Diffraction data for* $BaUF_6$.

I *	$\sin^2\theta$ (obs.)	$\sin^2\theta$ (calc.)	*hkl*	*I* *	$\sin^2\theta$ (obs.)	$\sin^2\theta$ (calc.)	*hkl*	*I* *	$\sin^2\theta$ (obs.)	$\sin^2\theta$ (calc.)	*hkl*
w	0·0424	0·0424	002	m−	0·1722	0·1721	112	vvw	0·3071	0·3075	105
w+	0·0431	0·0432	100	w+	0·1837	0·1835	201	w	0·3132	0·3132	211
s	0·0538	0·0538	101	vvw	0·2118	0·2127	104	vvw	0·3455	0·3449	212
w	0·0856	0·0856	102	w−	0·2684	0·2681	203	vw	0·3888	0·3891	300
m	0·1298	0·1297	110	w−	0·2990	0·2988	114	vw	0·3973	0·3977	213
m	0·1385	0·1385	103	vvw	0·3027	0·3026	210	vw	0·4314	0·4314	302
vvw	0·1694	0·1694	004								

* *I* = intensity.

In the BaF_2–UF_4 system a new phase appears at approximately 60 moles % of uranium tetrafluoride. The *X*-ray diffraction pattern of this has so far not been indexed. The $\sin^2\theta$ and intensity values are listed in Table 4. Thus between 50 and 60 moles % of uranium tetrafluoride the diffraction photographs show two phases, the new phase and

TABLE 4. *Compound formed at* 60 *moles* % *of* UF_4 *in the system* BaF_2–UF_4.

I *	$\sin^2\theta$	*I* *	$\sin^2\theta$	*I* *	$\sin^2\theta$	*I* *	$\sin^2\theta$
w+	0·0116	m−	0·0368	vw	0·0513	w+	0·0719
vvw	0·0172	m−	0·0396	w+	0·0527	vvw	0·0794
w+	0·0214	m+	0·0425	m+	0·0540	m−	0·0824
vw	0·0317	m−	0·0444	m+	0·0562	vw	0·0892
m−	0·0353	m−	0·0503	vw	0·0688	w−	0·1100

* *I* = intensity.

XUM

barium uranium hexafluoride. Again, the region from 60 to 100 moles % of uranium tetrafluoride is two-phase, the new phase and uranium tetrafluoride.

No similar phase appears in the SrF_2–ThF_4 system: between 50 and 100 moles % of thorium tetrafluoride the diffraction photographs show only two phases, strontium thorium hexafluoride and thorium tetrafluoride.

No evidence of solid solubility of the new compound in uranium tetrafluoride or of strontium thorium hexafluoride in thorium tetrafluoride is found.

The authors thank Mrs. G. W. Stuart for taking the *X*-ray photographs and for help in the experimental work.

Atomic Energy Research Establishment,
Harwell, Berkshire. [*Received, May 4th*, 1959.]

---

687. *Organosilyloxy-derivatives of Metals. Part I. Alkylsilyloxy-derivatives of Titanium, Zirconium, Niobium, and Tantalum.**

By D. C. Bradley and I. M. Thomas.

Compounds of the type $M(O{\cdot}SiMe_xEt_{3-x})_n$, $M(O{\cdot}SiMe_2Pr^n)_n$, and $M(O{\cdot}SiMe_2Pr^i)_n$ where $x = 3,2,1$, or 0, M = Ti, Zr, Nb, or Ta, and n is the valency of M, have been prepared by various methods. Their physicochemical properties have been studied and are compared with the corresponding metal tertiary alkoxides. The organosilyloxy–metal compounds appear to be less susceptible to hydrolysis or thermal decomposition than the metal tertiary alkoxides.

Tetrakistrimethylsilyloxytitanium $Ti(O{\cdot}SiMe_3)_4$ was first reported by English and Sommer [1] in 1955. Although other authors [2,3,4,5] have since prepared this and other trialkylsilyloxytitanium compounds, the yields were often low and little was known about them when our systematic studies began. Furthermore we have extended these studies to cover other transition metals whose trialkylsilyloxy-derivatives are more difficult to prepare. Now we report the preparation of derivatives of titanium, zirconium, niobium, and tantalum together with the results of molecular-weight studies (ebullioscopically in benzene) and boiling points under reduced pressure.

Preparative Methods.—English and Sommer's [1] synthesis of tetrakistrimethylsilyloxytitanium involved the reaction between titanium tetrachloride and trimethylsilanol in benzene in the presence of ammonia, and they inferred that the low yield (18%) was caused by water produced in the acid-catalysed condensation of the silanol. Zeitler and Brown [2] obtained a better yield (56%) by the silanolysis of titanium tetra-n-butoxide in boiling toluene:

$$4Me_3Si{\cdot}OH + Ti(OBu)_4 \longrightarrow Ti(O{\cdot}SiMe_3)_4 + 4BuOH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (I)$$

They isolated butoxytrimethylsilane among the products and it was thus clear that condensation of the silanol with the butyl alcohol liberated by silanolysis also produced water which hydrolysed the titanium compounds. This behaviour confirmed our independent experiences with the trimethylsilanolysis of titanium or zirconium isopropoxides and it was clear that good yields of these trimethylsilyloxy-derivatives would only result under conditions which suppressed the condensation reactions of the silanol. Obviously the concentrations of silanol and liberated alcohol (in the silanolysis) must be minimised. By

* Paper read at the International Conference on Co-ordination Chemistry, London, April, 1959.

[1] English and Sommer, *J. Amer. Chem. Soc*, 1955, **77**, 170.
[2] Zeitler and Brown, *ibid.*, 1957, **79**, 170.
[3] Dolgov and Orlov, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1957, 1395; *Doklady. Akad. Nauk S.S.S.R.*, 1957, **117**, 617.
[4] Andrianov, Zhdanov, Kurasheva, and Dvlova, *Doklady Akad. Nauk S.S.S.R.*, 1957, **112**, 1050.
[5] Bradley and Thomas, *Chem. and Ind.*, 1958, 17.

slow addition of the silanol in benzene to a boiling solution of the metal alkoxide in benzene, and constant removal of the liberated alcohol by azeotropic distillation, the titanium compound was quantitatively produced and the zirconium compound obtained in 70% yield. The pentakistrimethylsilyloxy-derivatives of niobium and tantalum were similarly obtained in 50% yield, whilst with the higher silanols, which are less readily condensed, practically quantitative yields were obtained with the four metals. Further evidence of the condensation of trimethylsilanol was obtained during attempts to reverse the silanolysis (1) by addition of n-butyl alcohol to tetrakistrimethylsilyloxytitanium, whereupon water appeared with the liberated silanol and the yield of titanium butoxide was low. It was interesting that silanolysis of trimethylsilyloxy-derivatives in boiling hexamethyldisiloxane does not cause condensation, and quantitative yields of trialkylsilyloxy-derivatives are afforded by this new method:

$$M(O{\cdot}SiMe_3)_n + nR_3Si{\cdot}OH \longrightarrow M(O{\cdot}SiR_3)_n + nMe_3Si{\cdot}OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In a preliminary communication [6] we have also reported another new general method of preparation based on trans-esterification: condensation is eliminated by using the trialkylsilyl acetate in place of the silanol and the reaction is conducted in boiling cyclohexane with which isopropyl or ethyl acetate forms minimum-boiling azeotropes. A quantitative yield of tetrakistrimethylsilyloxytitanium was thus obtained:

$$Ti(OR)_4 + 4Me_3Si{\cdot}OAc \longrightarrow Ti(O{\cdot}SiMe)_4 + 4ROAc \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The corresponding zirconium and tantalum compounds were obtained in 56% and 75% yields respectively. Even in this method it is important to add the trimethylsilyl acetate in cyclohexane slowly to the metal alkoxide because the silyl acetate appears to acetylate the silyloxy–metal compound when present in excess. With the higher alkylsilyl acetates two features were apparent: first, the rate of reaction (3) decreases with increase in size of the organosilyl group and secondly the tendency to cause acetylation also decreases, and it seems probable that steric effects are playing an important rôle. An interesting feature of reaction (3) is its apparent irreversibility. Thus tetrakistrimethylsilyloxytitanium and n-butyl acetate were heated in boiling toluene for 6 hr. but trimethylsilyl acetate could not be detected. On the other hand, metal alkoxides undergo reversible trans-esterification with alkyl acetates.

Properties of Alkylsilyloxy–Metal Compounds.—The alkylsilyloxy-compounds were colourless liquids or white solids which could be distilled or sublimed under reduced pressure. In Table 1 are presented the melting points, boiling points, and degrees of

TABLE 1.

	Ti			Zr			Ta		
Alkylsilyl oxide	M. p.	B. p./mm.	n	M. p.	B. p./mm.	n	M. p.	B. p./mm.	n
Me_3SiO	L	60°/0·1	1·21	152°	135°/0·1 *	2·05	80°	84°/0·05	1·08
Me_2EtSiO	L	86/0·1	1·00	105	105/0·1	1·20	135	135/0·1 *	0·98
$MeEt_2SiO$	L	120/0·1	0·99	30	120/0·1	1·05	180	170/0·1 *	1·00
Et_3SiO	110°	150/0·1	1·00	L	147/0·1	0·98	210	210/0·1 *	0·98
$Pr^n Me_2SiO$	L	112/0·2	0·99	60	103/0·05	1·11	L	170/0·1	1·00
$Pr^i Me_2SiO$	L	115/0·2	1·00	L	110/0·1	1·01	180	165/0·1 *	1·02

L = Liquid. * Sublimes.

polymerisation (n) for the ethylmethylsilyloxy- and isomeric dimethylpropylsilyloxy-titanium, -zirconium and -tantalum compounds. The melting points of the ethylmethylsilyloxy-series show some interesting trends. For titanium all except the triethylsilyloxy-compound are liquids, and for zirconium all except the triethylsilyloxy-compound are solids. For zirconium the melting point decreases steadily as methyl groups are replaced by ethyl but for tantalum the reverse occurs. Similarly, with zirconium the dimethyl-n-propylsilyloxy-compound is a solid and the isopropyldimethylsilyloxy-compound is a

[6] Bradley and Thomas, *Chem and Ind.*, 1958, 1231.

liquid but for tantalum the opposite is the case. It would be unwise to infer any structural implications from these data because some of the compounds are polymeric, but the extra alkylsilyloxy-group around the tantalum (cf. zirconium) clearly has important structural consequences. The most surprising feature is that in the triethylsilyloxy-compounds the titanium derivative has a fairly high melting point whilst the zirconium derivative is liquid, although both compounds are monomeric and very similar in volatility. Molecular-weight determinations have revealed some interesting facts. For example, among the titanium compounds the trimethylsilyloxy-derivative shows a significant degree of polymerisation whereas all of the others are monomeric. This result is particularly interesting because titanium tetra-t-butoxide is monomeric. In the zirconium compounds polymerisation is even greater and more extensive and it decreases steadily as methyl groups are replaced by ethyl, suggesting that steric effects operate. The latter point is further supported by the behaviour of the isomer dimethylpropylsilyloxy-zirconium as compared with that of the isomeric diethylmethylsilyloxy-derivative. Even in the trimethylsilyloxytantalum there is a small but significant degree of polymerisation whereas tantalum penta-t-butoxide is monomeric. This contrast in structural behaviour between trialkylsilyloxy-derivatives and the corresponding tertiary alkoxides demands explanation. Extensive studies on the metal alkoxides [7] showed that the decrease in degree of polymerisation with increased branching of the alkyl groups was mainly due to the steric effect of the alkyl groups and this must be a fundamental structural phenomenon which should operate also in the trialkylsilyloxy-derivatives. However, the replacement of the carbinol carbon atoms of the tertiary alkoxide by silicon atoms must cause some electronic disturbance, especially as partial double bonding involving donation of electrons from a p_π orbital of oxygen to a vacant d_π orbital of silicon may occur. The latter effect will be partly offset by the greater electronegativity of carbon compared with silicon but the fact that trimethylsilanol is more acidic than t-butyl alcohol suggests that the trimethylsilyloxy-group is more electron-attracting than the t-butoxy-group. It seems reasonable to suppose that the strength of intermolecular bonds involving metal and oxygen in these types of compound will increase with the electron density on the donor oxygen. This being accepted, it follows that from the electronic point of view a trialkylsilyloxy–metal compound should form less stable polymers than the corresponding metal t-alkoxide because of the reduced electron density on the oxygen in $R_3Si^{-}=^{+}O-$ compared with that of the oxygen in $R_3C{\cdot}O{\cdot}$. The experimental results thus indicate that steric effects must be the cause of the higher degree of polymerisation of trialkylsilyloxy-zirconium compared with the corresponding zirconium t-alkoxides. This is interesting because the silicon atoms will provide better shielding of the metal than the smaller carbinol carbon atoms. The smaller net shielding ability of the trialkylsilyloxy-group compared with the corresponding t-alkoxy-group may be caused by two factors. First, the Si–O bond's being longer than the C–O causes the alkyl groups in $R_3Si{\cdot}O{\cdot}M$ to be slightly further from the metal than in $R_3C{\cdot}O{\cdot}M$ and our studies on the metal alkoxides [7] have shown that the nearer that chain branching is to the metal the more effective is the shielding given by the alkyl group. Secondly, the partial double bonding $^{-}Si{=}O^{+}$ may result in the SiOM bond angle's being larger than $\angle$COM with consequent decrease in shielding power of the R_3SiO group. In addition to the data in Table 1 we have other evidence which suggests that the steric effects of R_3SiO groups are smaller than for R_3CO groups. In the alcoholysis of niobium or tantalum primary alkoxides with secondary or tertiary alcohols it appears that steric factors cause difficulties in replacing the fifth alkoxide group and compounds of the type $Ta(OR)(OR')_4$, where R = primary and R′ = secondary or tertiary alkyl, can be isolated.[8] However, we found no difficulty in replacing all of the ethoxy-groups in niobium or tantalum pentaethoxide with the trialkylsilyloxy-groups.

The importance of polymerisation in the lower trialkylsilyloxy-derivatives of titanium

[7] Bradley, Mehrotra, and Wardlaw, *J.*, 1952, 2027, and later papers in this series.
[8] Bradley, Chatterjee, Chakravarti, Wardlaw, and Whitley, *J.*, 1958, 99.

and zirconium is also apparent when their volatilities (Table 1) are compared together and with the corresponding t-alkoxides. Thus $Zr(O{\cdot}SiMe_3)_4$ is considerably less volatile than $Ti(O{\cdot}SiMe_3)_4$ which is also a little less volatile than the monomeric $Ti(O{\cdot}CMe_3)_4$ (b. p. 54°/0·1 mm.). The monomeric trialkylsilyloxy-derivatives of titanium and zirconium have very similar volatilities with a suggestion that the zirconium compounds are slightly the more volatile. Also the monomeric organosilyloxy-compounds appear to be slightly more volatile than the corresponding t-alkoxides and these facts are of importance in connection with the fundamental effect of mass on volatility.[9] This aspect of the work will be discussed later when more extensive vapour-pressure measurements are available.

Attempts to prepare niobium penta-t-alkoxides were unsuccessful owing to the tendency of these compounds to form the oxyalkoxides $Nb_2O(OR)_8$, and it was believed that the decomposition was promoted by the electron-releasing tendency of the t-alkyl groups.[10] In this work we obtained pentakistrimethylsilyloxyniobium which was distilled without decomposition at 120°/0·1 mm. and niobium pentakisdiethylmethylsilyloxyniobium which was sublimed at 140°/10^{-4} mm. There is little doubt that other organosilyloxyniobium compounds could also be obtained and their higher stability than of the t-alkoxides is consistent with the suggestion that the electron-releasing tendency of the trialkylsilyl group is counteracted by the d_π–p_π bonding between silicon and oxygen.

The organosilyloxy-derivatives of titanium, zirconium, niobium, and tantalum are noticeably less susceptible to hydrolysis and have greater thermal stability than the corresponding metal t-alkoxides. The resistance to hydrolysis appears to be connected with the water-repellent properties of the organosilicon groups whilst the high thermal stability is undoubtedly due to the fact that tertiary alcohols undergo thermolytic dehydration to give 1 mole of water per mole of alcohol whereas the silanols on condensation give only 1 mole of water per *two* moles of silanol (the thermal decomposition of the metal t-alkoxide being due to a hydrolytic chain reaction [11]).

Experimental

Preparation of Metal Alkoxides.—The alkoxides of titanium,[7] zirconium,[7] niobium,[12] and tantalum [13] were prepared by the literature methods and were freshly distilled under reduced pressure immediately before use.

Preparation of the Silanols.—Except for trimethylsilanol, the organosilanols were obtained by alkaline hydrolysis of the appropriate organosilyl chloride which was prepared from commercial alkylethoxysilane or ethyl orthosilicate by the following general reaction sequence:

$$Me_nSi(OEt)_{4-n} \xrightarrow{RMgBr} Me_nR_{3-n}Si(OEt) \xrightarrow{HCl,\ aq.} Me_nR_{3-n}Si{\cdot}O{\cdot}SiR_{3-n}Me_n \xrightarrow[NH_4Cl]{H_2SO_4\ conc.} Me_nR_{3-n}SiCl$$

Trimethylsilanol was obtained by hydrolysis of trimethylfluorosilane by the method of Sommer *et al.*[14] The organosilanols, in ether, were dried (K_2CO_3), the ether was evaporated off under reduced pressure, and the silanol then distilled. The following b. p.s were recorded: $Me_3Si{\cdot}OH$, 98·5—99·0°/763 mm.; $Me_2EtSi{\cdot}OH$, 119·5—120°/774 mm.; $MeEt_2Si{\cdot}OH$, 137·5—138·5°/758 mm.; $Et_3Si{\cdot}OH$, 167°/763 mm.; $Me_2Pr^nSi{\cdot}OH$, 137—138·5°/740 mm.; $Me_2Pr^iSi{\cdot}OH$, 131—132°/746 mm. For work involving the silanols the apparatus was rinsed first with alcoholic sodium hydroxide solution, and then distilled water, before being dried at 140°. The alkaline rinse proved an effective precaution against the ready acid-catalysed condensation of the silanol.

Preparation of Organosilyl Acetates.—Since the organosilyl chlorides were prepared as intermediates for the silanols they were conveniently used for preparing organosilyl acetates. Trimethylsilyl acetate (b. p. 102·5—103°/740 mm.) was obtained by the method of Schuyten *et al.*[15] by reaction between anhydrous sodium acetate and trimethylchlorosilane in ether

[9] Bradley, *Nature*, 1954, **174**, 323.
[10] Bradley, Chakravarti, and Wardlaw, *J.*, 1956, 4439.
[11] Bradley and Faktor, *J. Appl. Chem.*, in the press; *Trans. Faraday Soc.*, in the press.
[12] Bradley, Chakravarti, and Wardlaw, *J.*, 1956, 2381.
[13] Bradley, Whitley, and Wardlaw, *J.*, 1955, 726.
[14] Sommer, Pietrusza, and Whitmore, *J. Amer. Chem. Soc.*, 1946, **68**, 2282.
[15] Schuyten, Weaver, and Reid, *ibid.*, 1947, **69**, 2110.

(Found: OAc, 44·5. Calc. for $CH_3{\cdot}CO_2SiMe_3$: OAc, 44·7%). This procedure was not suitable for preparing the higher organosilyl acetates which were obtained as follows: The chlorosilane was heated at just below reflux temperature with excess of sodium acetate for 3 hr. The liquid obtained by decantation was fractionally distilled to give the organosilyl acetate. The following results were obtained: $CH_3{\cdot}CO_2SiMe_2Et$, b. p. 127—128°/746 mm. (Found: OAc, 40·1. Calc., 40·3%). $CH_3{\cdot}CO_2SiMeEt_2$, b. p. 150—151·5°/732 mm. (Found: OAc, 36·7. Calc., 36·9%). $CH_3{\cdot}CO_2SiEt_3$, b. p. 168·5—169·0°/765 mm. (Found: OAc, 33·8. Calc., 33·9%). Although the organosilyl acetates are readily hydrolysed it was possible to store them in stoppered bottles. The acetate determinations were carried out by titration of the hydrolysed sample with standard alkali after allowing 10 min. for completion of the hydrolysis.

Analytical Methods.—(i) *Metal.* The sample (*ca.* 0·3 g.) was weighed into a platinum crucible and dissolved in ethyl alcohol (2 c.c.). Ammonia solution (*d* 0·88, 3 c.c.) was added and the mixture cautiously evaporated to dryness by using an infrared lamp. This procedure removed the silicon as volatile organosilanol and left the metal as the hydrated oxide which was then ignited and weighed as oxide. The zirconium analyses were not corrected for the hafnium present (0·2—2·0%) but the error is not likely to exceed 0·5% of the zirconium figure.

(ii) *Silicon.* The sample (*ca.* 0·3 g.) was weighed into a beaker (400 c.c.) containing sulphuric acid (*d* 1·84, 30 c.c.) and ammonium nitrate (5 g.) and ammonium sulphate (5 g.) were then added. The mixture was heated, gently at first to convert the organosilicon groups into silica, then more strongly to evaporate off the excess of nitric acid, and finally at about the b. p. for 2 hr. to render the silica insoluble. The cooled contents of the beaker were poured into water (300 c.c.) and the silica filtered off on paper (Whatman No. 41), washed well with water, and finally ignited and weighed. With the niobium and tantalum compounds the silica was always contaminated with traces of metal oxide and the true silica content was obtained by difference after the removal of silicon as the tetrafluoride by treatment with hydrofluoric acid (10%, 4 c.c.) and a few drops of sulphuric acid, followed by evaporation under the infrared lamp and ignition of the residue.

(iii) *Alkoxide.* Ethoxide or isopropoxide was determined by the chromic acid method of Bradley *et al.*[16] which was unaffected by the presence of the organosilyloxy-groups. This method was used to confirm that all the alkoxide had been replaced by organosilyloxy-groups.

Silanolysis of Metal Alkoxides.—When titanium isopropoxide and trimethylsilanol were refluxed in benzene under a fractionating column the production of water was indicated by the appearance of some ternary azeotrope of benzene–water–isopropyl alcohol. After the removal of the remaining isopropyl alcohol as the binary azeotrope (benzene), and then the solvent, some tetrakistrimethylsilyloxytitanium [47% yield; b. p. 69°/0·5 mm. Found: Ti, 11·9. Calc. for $Ti(O{\cdot}SiMe_3)_4$: Ti, 11·8%] was distilled out. The presence of water in the first distillate and the low yield indicated condensations of the reactive silanol. Similarly when zirconium isopropoxide was treated with trimethylsilanol as above, a white *solid* [Found: Zr, 23·0. $Zr(O{\cdot}SiMe_3)_4$ requires Zr, 20·4%], which could not be sublimed up to 150°/0·1 mm., was obtained and was evidently a hydrolysis product. In preparing organosilyloxy-metal derivatives the silanolysis was carried out as follows: The silanol (10% excess over theoretical quantity) in benzene (*ca.* 15 c.c.) was added during several hours to a freshly distilled sample of the metal alkoxide refluxing in benzene (*ca.* 70 c.c.) under a fractionating column to remove the liberated alcohol as it was formed as the binary azeotrope with benzene. By this means the concentrations of silanol and alcohol were kept low and condensation of the silanol avoided. After removal of the alcohol the solvent and excess of silanol were evaporated off under reduced pressure and the metal organosilyloxide finally distilled or sublimed out *in vacuo*. Since essentially the same technique was used in each preparation we present the experimental details in abbreviated form in Table 2.

The yields in Table 2 are based on the pure distillate and it is noteworthy that whereas all of the titanium compounds are obtained quantitatively, for zirconium, niobium, and tantalum the yield increases steadily as the tendency of the silanol to condense decreases. It is possible that still higher yields of the lower alkylsilyloxy-compounds could be obtained with a further modification of technique whereby solutions of silanol and of metal alkoxide were each added slowly to the refluxing solvent. By this means the concentration of metal alkoxide would also be kept low and the metal-alkoxide catalysed condensation of the silanol avoided. The lower yield of zirconium trimethylsilyloxide than of the titanium compound is probably due to the

[16] Bradley, Halim, and Wardlaw, *J.*, 1950, 3450.

TABLE 2.

Product	Silanol taken (g.)	Alkoxide taken (g.)	Yield (g.)	Yield (%)	Analyses Found (%) M	Found (%) Si	Calc. (%) M	Calc. (%) Si
$Ti(O{\cdot}SiMe_3)_4$	6·90	5·12 [a]	7·29	100	11·7	—	11·8	—
$Ti(O{\cdot}SiMe_2Et)_4$	6·80	4·27 [a]	6·49	94	10·4	24·5	10·4	24·4
$Ti(O{\cdot}SiMeEt_2)_4$	8·00	4·02 [a]	7·17	98	9·31	21·7	9·27	21·7
$Ti(O{\cdot}SiEt_3)_4$	9·50	4·80 [a]	9·02	94	8·40	19·6	8·36	19·6
$Ti(O{\cdot}SiMe_2Pr^n)_4$	19·8	10·2 [a]	18·3	99	9·29	21·6	9·27	21·7
$Ti(O{\cdot}SiMe_2Pr^n)_4$	19·5	10·1 [a]	18·0	98	9·20	21·7	,,	,,
$Zr(O{\cdot}SiMe_3)_4$	7·90	5·93 [b]	5·93	73	20·4	—	20·4	—
$Zr(O{\cdot}SiMe_2Et)_4$	18·5	13·2 [c]	14·3	79	18·2	22·1	18·1	22·3
$Zr(O{\cdot}SiMeEt_2)_4$	10·5	5·98 [b]	9·58	95	16·5	20·0	16·3	20·0
$Zr(O{\cdot}SiEt_3)_4$	11·5	6·69 [b]	12·4	99	14·9	18·2	14·8	18·2
$Zr(O{\cdot}SiMe_2Pr^n)_4$	21·0	14·4 [c]	16·9	81	16·2	20·0	16·3	20·0
$Zr(O{\cdot}SiMe_2Pr^i)_4$	11·0	7·30 [c]	10·1	91	16·2	20·1	,,	,,
$Ta(O{\cdot}SiMe_3)_5$	4·70	4·15 [d]	3·27	48	28·9	22·4	28·9	22·4
$Ta(O{\cdot}SiMe_2Et)_5$	6·50	4·64 [d]	6·55	82	26·0	20·3	25·9	20·1
$Ta(O{\cdot}SiMeEt_2)_5$	8·30	5·37 [d]	8·70	86	23·6	18·2	23·6	18·3
$Ta(O{\cdot}SiEt_3)_5$	9·00	4·09 [d]	8·23	96	21·6	16·7	21·6	16·8
$Ta(O{\cdot}SiMe_2Pr^n)_5$	5·00	2·51 [d]	4·30	91	23·6	18·4	23·6	18·3
$Ta(O{\cdot}SiMe_2Pr^i)_5$	9·00	5·62 [d]	9·95	95	23·8	18·2	,,	,,
$Nb(O{\cdot}SiMe_3)_5$	2·62	1·81 [e]	1·57	54	17·4	—	17·2	—
$Nb(O{\cdot}SiMeEt_2)_5$	4·40	2·13 [e]	4·09	90	13·7	20·4	13·6$_5$	20·6$_5$

[a] $Ti(OPr^i)_4$, [b] $Zr(OPr^i)_4$, [c] $Zr(OBu^t)_4$, [d] $Ta(OEt)_5$, [e] $Nb(OEt)_5$.

fact that zirconium alkoxides are stronger " Lewis-acids " than titanium alkoxides and also because the zirconium compounds are more readily hydrolysed.

Silanolysis of Metal Trimethylsilyloxides.—These reactions were carried out similarly to silanolyses of the metal alkoxide except that hexamethyldisiloxane was used as solvent because it forms a convenient minimum-boiling azeotrope with trimethylsilanol. The higher silanol in hexamethyldisiloxane (*ca.* 15 c.c.) was added slowly to the boiling solution of metal trimethylsilyloxide in hexamethyldisiloxane (*ca.* 120 c.c.) and the liberated trimethylsilanol removed by fractionation. The higher alkylsilyloxy-metal compound was finally isolated by vacuum distillation. Details are in Table 3.

TABLE 3.

Product	Silanol taken (g.)	$M(O{\cdot}SiMe_3)_x$ (g.)	Yield of product (g.)	Yield of product (%)	Found (%) M	Found (%) Si
$Ti(O{\cdot}SiMe_2Et)_4$	10·0	6·90	7·85	100	10·4	24·2
$Ti(O{\cdot}SiMeEt_2)_4$	8·40	6·72	7·71	90	9·27	21·6
$Ti(O{\cdot}SiEt_3)_4$	6·00	4·18	5·57	94	8·37	19·5
$Zr(O{\cdot}SiMe_2Et)_4$	6·75	4·77	5·20	97	18·2	22·4
$Zr(O{\cdot}SiEt_3)_4$	5·30	4·22	5·28	91	14·9	18·2
$Ta(O{\cdot}SiMe_2Et)_5$	2·00	1·72	1·80	94	26·0	20·4
$Ta(O{\cdot}SiMeEt_2)_5$	1·70	1·59	1·90	98	23·6	18·2
$Ta(O{\cdot}SiEt_3)_5$	3·25	3·02	3·55	88	21·6	16·8

It is noteworthy that these reactions are all practically quantitative in spite of the fact that the reactive trimethylsilanol is liberated in each case and it appears that the metal alkylsilyloxides do not catalyse its condensation.

Reaction between Tetrakistrimethylsilyloxytitanium and n-Butyl Alcohol.—To the titanium compound (5·45 g.) in boiling toluene (70 c.c.) was slowly added a solution of n-butyl alcohol (8·0 g.) in toluene (20 c.c.) and the mixture was fractionated. Water was detected in the distillate, and after about 3 hr. pure solvent was collected. Removal of excess of solvent under reduced pressure left a liquid (3·40 g.) which was free from silicon. A sample (3·00 g.) heated under reduced pressure gave some *titanium tetrabutoxide* [1·00 g. Found: Ti, 14·3. $Ti(OBu)_4$ requires Ti, 14·1%]. The presence of water in the volatile products and the low yield of titanium butoxide confirmed that the silanol undergoes condensation in the presence of the metal alkoxide and the butyl alcohol.

Reactions involving Metal Alkoxides and Organosilyl Acetates.—(i) *Titanium isopropoxide and trimethylsilyl acetate.* Titanium isopropoxide (2·12 g.) and trimethylsilyl acetate (10·4 g.) were refluxed under a fractionating column and during the first 15 min. isopropyl acetate was distilled

out. After about 35 min. the liberation of isopropyl acetate was practically complete and a solid separated. The fine white powder (2·20 g.) remaining after the removal of excess of trimethylsilyl acetate contained no isopropoxide but a large amount of acetate (Found: Ti, 24·0; OAc, 36·3; Si, 3·7%).

(ii) *Tetrakistrimethylsilyloxytitanium and trimethylsilyl acetate.* From the foregoing reaction it appeared that although a trans-esterification occurs initially, the metal trimethylsilyloxide becomes acetylated by the excess of trimethylsilyl acetate. This was proved when tetrakistrimethylsilyloxytitanium (5·0 g.) was refluxed with trimethylsilyl acetate (10·0 g.) under similar conditions to the previous experiment. Solid was slowly precipitated and had a composition similar to the product of the previous reaction (Found: Ti, 23·7; OAc, 42·7; Si, 1·8%).

(iii) *Preparation of metal organosilyloxides.* The foregoing acetylation side-reactions were avoided by using only the theoretical quantity of organosilyl acetate and conducting the reactions in cyclohexane which forms minimum-boiling azeotropes with either ethyl or isopropyl acetate. Trimethylsilyl acetate was added slowly as a solution in cyclohexane (*ca.* 20 c.c.) to the metal alkoxide in cyclohexane (*ca.* 120 c.c.), and the alkyl acetate fractionated out as it formed. With the higher alkylsilyl acetates the trans-esterification is much slower and acetylation less important; hence the whole of the reactants were added together at the beginning of the reaction. In general the trans-esterifications required much longer than the corresponding silanolyses for completion. The products were isolated in the usual way and details are in Table 4.

The reversibility of the trans-esterification was explored by heating tetrakistrimethylsilyloxytitanium (2·57 g.) and n-butyl acetate (3·0 g.) in toluene (70 c.c.) under a fractionating column. Toluene was the sole constituent of the distillate during 6 hr. and the failure to produce trimethylsilyl acetate and titanium butoxide was confirmed when the solvent and n-butyl acetate were distilled off leaving the original titanium compound (Found: Ti, 11·8%).

Molecular-weight Determinations.—Some measurements were carried out in boiling benzene

TABLE 4.

Product	Acetate taken (g.)	Alkoxide taken (g.)	Yield (g.)	Yield (%)	Reaction time (hr.)	Found, % M	Found, % Si
$Ti(O{\cdot}SiMe_3)_4$	56·0	29·4 [a]	39·7	95	10	12·0	—
$Ti(O{\cdot}SiMe_2Et)_4$	18·0	8·37 [a]	13·1	97	9	10·4	24·0
$Ti(O{\cdot}SiMeEt_2)_4$	18·5	7·67 [a]	13·3	96	35	9·37	21·7
$Ti(O{\cdot}SiEt_3)_4$	12·0	3·90 [a]	7·75	93	132	8·40	19·5
$Zr(O{\cdot}SiMe_3)_4$	26·0	15·2 [b]	11·5	56	28	20·4	—
$Zr(O{\cdot}SiMe_2Et)_4$	11·6	6·20 [b]	7·64	80	10	18·2	22·1
$Zr(O{\cdot}SiMeEt_2)_4$	13·0	5·79 [b]	9·11	92	18	16·4	20·1
$Zr(O{\cdot}SiEt_3)_4$	9·00	2·81 [b]	4·75	90	132	14·9	18·2
$Ta(O{\cdot}SiMe_3)_5$	19·5	11·8 [d]	13·4	74	18	28·9	22·2
$Ta(O{\cdot}SiMe_2Et)_5$	17·0	3·68 [d]	5·56	88	8	26·0	20·1
$Ta(O{\cdot}SiMeEt_2)_5$	10·0	4·40 [d]	5·97	72	30	23·6	18·4

a, *b*, *d* As in Table 2.

in an all-glass ebulliometer incorporating a differential water thermometer of the type previously described.[17] The internal calibration method [18] with pure fluorene was used with 15—16 g. of benzene per experiment. Although approximately fivefold ranges of concentration were covered, the apparent molecular weight was independent of concentration. Results are in Table 5 (*m* is the weight of solute).

TABLE 5.

	Metal organosilyloxide		Fluorene		*M*	
Compound	Range in *m* (g.)	$\Delta T/m$(°/g.)	Range in *m* (g.)	$\Delta T/m$(°/g.)	Found	Calc.
$Ti(O{\cdot}SiMe_3)_4$	0·0523—0·2720	0·357	0·0270—0·1200	1·050	488	404·9
$Ti(O{\cdot}SiMeEt_2)_4$	0·0810—0·3770	0·346	0·0460—0·1520	1·059	508	516·8
$Ti(O{\cdot}SiEt_3)_4$	0·2660—0·6850	0·333	0·2054—0·3711	1·139	569	572·9
$Zr(O{\cdot}SiEt_3)_4$	0·0840—0·4100	0·279	0·0480—0·1440	1·012	602	616·2

The majority of measurements were made with a new all-glass ebulliometer incorporating a multi-junction differential thermocouple constructed by H. Holloway (to be described in a

[17] Bradley, Gaze, and Wardlaw, *J.*, 1955, 3977.
[18] Bradley, Whitley, and Wardlaw, *J.*, 1956, 5.

later communication). The internal calibration method was used with either fluorene or diphenyl and the results are in Table 6. About 16—18 g. of benzene were used per experiment.

One difficulty experienced in this work was the tendency of boiling benzene solutions of metal organosilyloxides to froth. This was originally ascribed to the presence of traces of

TABLE 6.

Metal organosilyloxide			Calibrant		*M*	
Compound	Range in *m* (g.)	$\Delta T/m$ *	Range in *m* (g.)	$\Delta T/m$ *	Found	Calc.
$Ti(O{\cdot}SiMe_2Et)_4$	0·2340—1·155	296	0·0961—0·4682 †	889	462	460·7
$Ti(O{\cdot}SiMe_2Pr^i)_4$	0·1250—0·6159	165	0·0320—0·1204 ‡	511	516	516·8
$Ti(O{\cdot}SiMe_2Pr^n)_4$	0·0658—0·5854	166	0·0148—0·1017 ‡	510	511	516·8
$Zr(O{\cdot}SiMe_3)_4$	0·1190—1·442	126	0·1823—0·4201 †	750	916	447·9
$Zr(O{\cdot}SiMe_2Et)_4$	0·1776—0·5717	148	0·0321—0·0994 ‡	536	602	504·0
$Zr(O{\cdot}SiMe_2Pr^i)_4$	0·1127—0·6073	151	0·0101—0·1238 ‡	516	568	560·1
$Zr(O{\cdot}SiMe_2Pr^n)_4$	0·0763—0·5943	140·5	0·0472—0·1208 ‡	525	621	560·1
$Zr(O{\cdot}SiMeEt_2)_4$	0·0977—0·6224	146·5	0·0225—0·1336 ‡	517	586	560·1
$Ta(O{\cdot}SiMe_3)_5$	0·2037—0·8597	117	0·0517—0·1736 ‡	478	678	626·7
$Ta(O{\cdot}SiMe_2Et)_5$	0·2520—1·200	181	0·0832—0·1960 †	800	681	696·8
$Ta(O{\cdot}SiMe_2Pr^i)_5$	0·1702—0·9947	114·5	0·0200—0·0794 ‡	540	783	767·0
$Ta(O{\cdot}SiMe_2Pr^n)_5$	0·1107—0·7643	115	0·0351—0·1325 ‡	530	765	767·0
$Ta(O{\cdot}SiMeEt_2)_5$	0·1178—0·3440	175·5	0·0240—0·1908 †	870	763	767·0
$Ta(O{\cdot}SiEt_3)_5$	0·1371—0·5709	202	0·0820—0·3503 †	1080	824	837·1

* In arbitary e.m.f. units/g.; † diphenyl; ‡ fluorene.

silicone vacuum grease acquired during vacuum distillation of the metal compound immediately before the ebullioscopic measurements. Nevertheless, in spite of extreme precautions taken to avoid contamination by Silicone the frothing remained and it is concluded that the metal organosilyloxides are surface-active in benzene. By improving the thermal insulation of the apparatus and using low boil-up rates the degree of frothing was not allowed to impair the accuracy of the measurements. The results are very probably accurate to within 5% and probably to within 2%, so that the small degrees of polymerisation found with $Ti(O{\cdot}SiMe_3)_4$, $Zr(O{\cdot}SiMe_2Et)_4$, $Zr(O{\cdot}SiMe_2Pr^n)_4$, $Ta(O{\cdot}SiMe_3)_5$, and possibly with $Zr(O{\cdot}SiMeEt_2)_4$ are significant.

We thank the Bradford Dyers Association Ltd. for a research grant (to I. M. T.) and the late Professor Wardlaw for his interest and encouragement.

BIRKBECK COLLEGE, MALET STREET, LONDON, W.C.1. [*Received, May 8th*, 1959.]

---

688. *Hydropteridines. Part V.*[1] 7,8-*Dihydro*-6-*hydroxypteridine*-4-*carboxylic Acids.*

By JIM CLARK and A. J. LAYTON.

The preparation of some 2-substituted 7,8-dihydro-6-hydroxypteridine-4-carboxylic acids and their ethyl esters is described.

MANY pteridine-6- and -7-carboxylic acids have been described. Some were isolated from natural sources[2] while others have been synthesised. Synthetical routes include condensation of 4,5-diaminopyrimidines with dicarbonyl compounds such as ethyl mesoxalate,[3,4] and reaction of 4-amino-5-nitrosopyrimidines with ethyl malonate or cyanoacetate.[5] Pteridine-6- and -7-carboxylic acids have also been obtained by oxidation

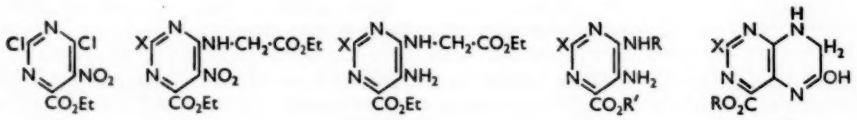
[1] Brook and Ramage, Part IV, *J.*, 1957, 1.
[2] Forrest and Mitchell, *J. Amer. Chem. Soc.*, 1955, **77**, 4865. Viscontini, Schoeller, Loeser, Karrer, and Hadorn, *Helv. Chim. Acta*, 1955, **38**, 397.
[3] Purrmann, *Annalen*, 1941, **548**, 284; Elion, Hitchings, and Russell, *J. Amer. Chem. Soc.*, 1950, **72**, 78. Elion and Hitchings, *ibid.*, 1953, **75**, 4311.
[4] Whittle, O'Dell, Vandenbelt, and Pfiffner, *J. Amer. Chem. Soc.*, 1947, **69**, 1786.
[5] Osdene and Timmis, *J.*, 1955, 2036.

XUM

of suitable 6- or 7-substituted pteridines.[4,6,7] These acids have been used as reference compounds for the identification of degradation products of pteridine pigments [7,8] and pteroylglutamic acid and related compounds.[4,9]

Although many 6- and 7-carboxylic acids are well known, no pteridine-2- or -4-carboxylic acid has been reported. The lack of suitable pyrimidine intermediates has been partly responsible but 2,6-dichloro-5-nitropyrimidine-4-carboxylic esters [10] now provide starting materials for the synthesis of pteridine-4-carboxylic acids.

Ethyl 2,6-dichloro-5-nitropyrimidine-4-carboxylate (I) has been converted into 7,8-dihydro-6-hydroxypteridine-4-carboxylic acids by a route which is essentially that used by Boon, Jones, and Ramage [11] to prepare 6-hydroxypteridines. The dichloro-compound (I) was condensed with ethyl aminoacetate, and the 2-chlorine atom of the product (II; X = Cl) replaced by a variety of groups. An amino- or dimethylamino-group was introduced by reaction with the appropriate amine, and a hydroxyl group by reaction with boiling acetate buffer, whilst treatment with sodium sulphide and sodium hydrogen carbonate yielded the 2-mercapto-derivative (II; X = SH). The corresponding 2-ethoxy-compound was obtained by boiling the chloro-compound with ethanol and an equivalent of pyridine.



(I) (II) (III) (IV) (V)

Use of Raney nickel and hydrogen to reduce the 5-nitropyrimidines was less satisfactory than for similar pyrimidines with no ester group,[11] and this reflected the experience of Clark and Ramage [10] in reductions of 6-2′-chloroethylamino-5-nitropyrimidine-4-carboxylic esters. Reduction by sodium dithionite in sodium hydrogen carbonate solution gave good results except for the 2-chloro-compound (II; X = Cl) which was better reduced by zinc and a little acetic acid in methanol. Chloroform solutions of some 5-aminopyrimidines (III; X = Cl, OH, or OEt) exhibited a strong blue and others (III; X = NH_2 or NMe_2) a strong green fluorescence in ultraviolet light but the 2-mercapto-compound (III; X = SH) was not fluorescent. Fluorescence appears to be a general property of 5,6-diaminopyrimidine-4-carboxylic esters for it was shown by the above compounds, by 5-amino-6-2′-chloroethylaminopyrimidine-4-carboxylic esters (IV; R = CH_2·CH_2Cl),[10] by 6-acetonylamino-5-aminopyrimidine-4-carboxylic esters (IV; R = CH_2Ac),[12] and by 5,6-diaminopyrimidine-4-carboxylic esters (IV; R = H).[12] The pronounced effect, frequently visible in daylight, appeared immediately reduction of the 5-nitro-compounds was commenced and so was unlikely to be due to oxidative self-condensation reactions which can lead to fluorescent impurities in 5-amino-4-substituted-aminopyrimidines kept in non-reducing conditions.

The ethyl 5-amino-6-ethoxycarbonyl-4-pyrimidylaminoacetates (III) were sufficiently stable to be crystallised without interference by cyclisation and therefore differed from similar compounds with no ester group.[11] The less ready cyclisation of these compounds may have been due to the base-weakening effect of the ester group on the 5-amino-group

[6] Cain, Mallette, and Taylor, *J. Amer. Chem. Soc.*, 1948, **70**, 3026; Forrest and Walker, *J.*, 1949, 79, 2077; Backer and Houtman, *Rec. Trav. chim.*, 1951, **70**, 725.
[7] Tschesche and Korte, *Chem. Ber.*, 1951, **84**, 77.
[8] Hirata, Nawa, Matsuura, and Kakizawa, *Experientia*, 1952, **8**, 339.
[9] Stokstad, Hutchings, Mowat, Boothe, Waller, Angier, and Subba Row, *J. Amer. Chem. Soc.*, 1948, **70**, 5; Mowat, Boothe, Hutchings, Stokstad, Waller, Angier, Semb, Cosulich, and Subba Row, *ibid.*, p. 14.
[10] Clark and Ramage, *J.*, 1958, 2821.
[11] Boon, Jones, and Ramage, *ibid.*, 1951, 96.
[12] Clark, unpublished results.

and to hydrogen bonding. The compound (III; X = Cl), in which the base-weakening effect of the ester group was supplemented by that of a 2-chlorine atom, was the most stable.

With the exception of the last-named compound, which was recovered unchanged from boiling ethanol, water, or 2-ethoxyethanol, the 5-amino-4-pyrimidylaminoacetates were cyclised in water or aqueous ethanol. The chloro-compound (III; X = Cl) required dilute acetic acid to promote the reaction.

The resulting 7,8-dihydro-6-hydroxypteridinecarboxylic esters were readily hydrolysed by alkali to the corresponding acids but it was necessary to use mild conditions to prevent the easy cleavage of the dihydropyrazine rings of some of these compounds.

Experimental

Ethyl 2-Chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate (II; X = Cl).—Ethyl aminoacetate hydrochloride (15 g.) was added, with shaking, during 20 min. to a mixture of ethyl 2,6-dichloro-5-nitropyrimidine-4-carboxylate [10] (27 g.) in chloroform (250 c.c.) and sodium hydrogen carbonate (25 g.) in water (100 c.c.). Shaking was continued for a further 15 min. before the chloroform layer was separated, washed with water, dried, and evaporated. *Ethyl 2-chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate* (29 g.) crystallised from ethanol as needles, m. p. 99° (Found: C, 39·6; H, 4·0. $C_{11}H_{13}O_6N_4Cl$ requires C, 39·7; H, 3·9%).

Ethyl 5-Amino-2-chloro-6-ethoxycarbonyl-4-pyrimidylaminoacetate (III; X = Cl).—To a stirred solution of ethyl 2-chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate (4·5 g.) in methanol (120 c.c.) was added acetic acid (30 c.c.) immediately followed by powdered zinc (15 g.). The mixture was well stirred for 5 min. and quickly filtered. The residue was washed with warm methanol, and the combined filtrates concentrated under reduced pressure. Water (200 c.c.) was added, and *ethyl 5-amino-2-chloro-6-ethoxycarbonyl-4-pyrimidylaminoacetate* (3 g.) was filtered off and crystallised from ethanol as prisms, m. p. 178—180° (Found: C, 43·5; H, 4·9. $C_{11}H_{15}O_4N_4Cl$ requires C, 43·6; H, 5·0%).

Ethyl 2-Chloro-7,8-dihydro-6-hydroxypteridine-4-carboxylate (V; X = Cl, R = Et).—A solution of ethyl 5-amino-2-chloro-6-ethoxycarbonyl-4-pyrimidylaminoacetate (1 g.) in dilute acetic acid (50 c.c.) was heated under reflux for 1 hr. *Ethyl 2-chloro-7,8-dihydro-6-hydroxypteridine-4-carboxylate* (0·62 g.) was filtered off and crystallised from aqueous ethanol, forming needles which gradually decomposed above 250° (Found: C, 41·5; H, 3·5; Cl, 13·8. $C_9H_9O_3N_4Cl$ requires C, 42·1; H, 3·5; Cl, 13·8%).

An *acetyl* derivative crystallised from aqueous ethanol as blades, m. p. 153—154° (Found: C, 44·0; H, 3·7. $C_{11}H_{11}O_4N_4Cl$ requires C, 44·2; H, 3·7%); the picrate dissociated on recrystallisation.

Ethyl 2-Ethoxy-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate (II; X = OEt).—Ethyl 2-chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate (5 g.), ethanol (100 c.c.), and pyridine (1·3 c.c.) were heated under reflux for 3 hr. The cooled solution was acidified with N-hydrochloric acid and diluted with water, and *ethyl 2-ethoxy-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate* (4·6 g.) was washed with water and crystallised from ethanol, forming needles, m. p. 93—94° (Found: C, 46·0; H, 5·3. $C_{13}H_{18}O_7N_4$ requires C, 45·6; H, 5·3%).

Ethyl 2-Ethoxy-7,8-dihydro-6-hydroxypteridine-4-carboxylate (V; X = OEt, R = Et).—To a well-stirred solution of ethyl 2-ethoxy-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate (4·6 g.) in acetone (100 c.c.) was added sodium hydrogen carbonate (20 g.) in water (100 c.c.), followed by sodium dithionite (20 g.) added during 5 min. After a further 10 min. the mixture was diluted with water (200 c.c.) and extracted with chloroform. The extract was washed with water, dried, and evaporated to yield *ethyl 5-amino-2-ethoxy-6-ethoxycarbonyl-4-pyrimidylaminoacetate* (3·2 g.); a sample of which crystallised from benzene–cyclohexane as pale cream needles, m. p. 155° (with rapid heating) (Found: C, 50·0; H, 6·5. $C_{13}H_{20}O_5N_4$ requires C, 50·0; H, 6·5%).

This amine (3 g.) was heated in refluxing aqueous ethanol during 1 hr.; *ethyl 2-ethoxy-7,8-dihydro-6-hydroxypteridine-4-carboxylate* (2·2 g.) was filtered off and crystallised from aqueous ethanol, forming needles which gradually decomposed above 240° (Found: C, 49·1; H, 5·2. $C_{11}H_{14}O_4N_4$ requires C, 49·6; H, 5·3%).

A *monoacetyl* derivative crystallised from aqueous ethanol as needles, m. p. 150° (Found:

XUM

C, 50·4; H, 5·1; N, 18·5. $C_{13}H_{16}O_5N_4$ requires C, 50·6; H, 5·2; N, 18·2%). The *picrate* crystallised from ethanol, containing a little picric acid, as yellow needles, m. p. 182° (decomp.) (Found: C, 40·8; H, 3·5. $C_{11}H_{14}O_4N_4,C_6H_3O_7N_3$ requires C, 41·2; H, 3·5%).

Ethyl 2-Dimethylamino-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate (II; X = NMe_2).—A solution of 26% aqueous dimethylamine (2·2 c.c.) in ethanol (5 c.c.) was added dropwise to a stirred solution of ethyl 2-chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate (2 g.) in ethanol (30 c.c.), and the mixture stirred for a further 15 min. *Ethyl 2-dimethylamino-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate* was filtered off and crystallised from ethanol, forming needles (1·9 g.), m. p. 135° (Found: C, 46·1; H, 5·4. $C_{13}H_{19}O_6N_5$ requires C, 45·8; H, 5·6%).

Ethyl 2-Dimethylamino-7,8-dihydro-6-hydroxypteridine-4-carboxylate (V; X = NMe_2, R = Et).—Ethyl 2-dimethylamino-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate (5 g.) was reduced as described for the corresponding 2-ethoxy-compound, except that the resulting amino-derivative (3·6 g.) was recovered by filtration. *Ethyl 5-amino-2-dimethylamino-6-ethoxycarbonyl-4-pyrimidylaminoacetate* crystallised from benzene as greenish-yellow needles, m. p. 139° (Found: C, 50·3; H, 6·6. $C_{13}H_{21}O_4N_5$ requires C, 50·1; H, 6·8%). The *acetyl* derivative crystallised from water as needles, m. p. 123° (Found: C, 48·5; H, 6·7. $C_{15}H_{23}O_5N_5,H_2O$ requires C, 48·5; H, 6·8%).

The amine (1·0 g.) was cyclised in boiling water during 3 hr. and the resulting *ethyl 2-dimethylamino-7,8-dihydro-6-hydroxypteridine-4-carboxylate* (0·5 g.) crystallised from dioxan, forming greenish-yellow needles which gradually decomposed above 260° (Found: C, 49·6; H, 5·8. $C_{11}H_{15}O_3N_5$ requires C, 49·8; H, 5·7%).

A *monoacetyl* derivative crystallised from water as yellow needles, m. p. 177—178° (Found: C, 51·1; H, 5·8; N, 22·4. $C_{13}H_{17}O_4N_5$ requires C, 50·8; H, 5·6; N, 22·8%). The *picrate* crystallised from ethanol, containing a little picric acid, as yellow needles which gradually decomposed above 170° (Found: C, 41·5; H, 3·6. $C_{11}H_{15}O_3N_5,C_6H_3O_7N_3$ requires C, 41·3; H, 3·7%).

Ethyl 2-Amino-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate (II; X = NH_2).—A solution of ethyl 2-chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate (5 g.) in ethanol (25 c.c.) was treated with ammonia (1·67 c.c., s.g. 0·88) and the solution heated under reflux for ½ hr. *Ethyl 2-amino-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate* (4 g.) was filtered off and crystallised from ethanol, forming needles, m. p. 161° (Found: C, 41·8; H, 4·8. $C_{11}H_{15}O_6N_5$ requires C, 42·2; H, 4·7%).

Ethyl 2-Amino-7,8-dihydro-6-hydroxypteridine-4-carboxylate (V; X = NH_2, R = Et).—Ethyl 2-amino-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate (3 g.) was reduced as described for the corresponding 2-ethoxy-compound and yielded *ethyl 2,5-diamino-6-ethoxycarbonyl-4-pyrimidylaminoacetate* (2·1 g.) which crystallised from benzene as pale yellow needles, m. p. 171—172° (with rapid heating) (Found: C, 46·5; H, 5·8. $C_{11}H_{17}O_4N_5$ requires C, 46·6; H, 6·1%).

The diamine (1·25 g.) was cyclised in boiling water during 2 hr. and yielded ethyl 2-amino-7,8-dihydro-6-hydroxypteridine-4-carboxylate (0·55 g.) as a pale-brown amorphous powder (decomp. >230°) which did not dissolve in the usual solvents. Attempts to purify the material by precipitation from alkali led to hydrolysis of the ester group and so it was characterised as the corresponding carboxylic acid (below).

Ethyl 6-Ethoxycarbonyl-2-hydroxy-5-nitro-4-pyrimidylaminoacetate (II; X = OH).—A mixture of ethyl 2-chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate (2·5 g.), sodium acetate trihydrate (4 g.), water (7·5 c.c.), and acetic acid (7·5 c.c.) was heated under reflux during 15 min. *Ethyl 6-ethoxycarbonyl-2-hydroxy-5-nitro-4-pyrimidylaminoacetate* (1·6 g.) was filtered off from the cooled solution; a sample crystallised from water as needles, m. p. 190° (decomp.) (Found: C, 42·2; H, 4·4. $C_{11}H_{14}O_7N_4$ requires C, 42·0; H, 4·5%).

Ethyl 7,8-Dihydro-2,6-dihydroxypteridine-4-carboxylate (V; X = OH, R = Et).—Ethyl 6-ethoxycarbonyl-2-hydroxy-5-nitro-4-pyrimidylaminoacetate (1·6 g.) was reduced as described for the corresponding 2-ethoxy-compound, except that it was unnecessary to use acetone. The resulting *ethyl 5-amino-6-ethoxycarbonyl-2-hydroxy-4-pyrimidylaminoacetate* (0·82 g.) crystallised from tetrahydrofuran as prisms which gradually decomposed above 150° (Found: C, 46·1; H, 5·7. $C_{11}H_{16}O_5N_4$ requires C, 46·5; H, 5·7%).

The amine (1 g.) was cyclised in boiling water during 2 hr. and yielded *ethyl 7,8-dihydro-2,6-dihydroxypteridine-4-carboxylate* (0·5 g.) which crystallised from water as plates which

gradually decomposed above 240° (Found: C, 45·0; H, 4·0. $C_9H_{10}O_4N_4$ requires C, 45·4; H, 4·2%).

The *picrate* crystallised from water as yellow needles which gradually decomposed above 190° (Found: C, 38·6; H, 2·8. $C_9H_{10}O_4N_4,C_6H_3O_7N_3$ requires C, 38·6; H, 2·7%).

Ethyl 7,8-Dihydro-6-hydroxy-2-mercaptopteridine-4-carboxylate (V; X = SH, R = Et).—Ethyl 2-chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidylaminoacetate (5 g.) was stirred with a solution of sodium sulphide nonahydrate (4 g.) and sodium hydrogen carbonate (1·3 g.) in water (200 c.c.) and acetone (5 c.c.) for 3 hr; undissolved material was filtered off (*A*). Sodium hydrogen carbonate (18 g.) and sodium dithionite (20 g.) were added and after 10 min., *ethyl 5-amino-6-ethoxycarbonyl-2-mercapto-4-pyrimidylaminoacetate* (3·4 g.) was filtered off. A sample crystallised from ethanol as yellow prisms, m. p. 161—162° (Found: C, 43·4; H, 5·4. $C_{11}H_{16}O_4N_4S$ requires C, 44·0; H, 5·4%).

This amine (1 g.) was cyclised as described for the corresponding 2-amino-compound and the product, ethyl 7,8-dihydro-6-hydroxy-2-mercaptopteridine-4-carboxylate (0·7 g.), was a similarly intractable solid (yellow) which gradually decomposed above 230°. It was not possible to purify it by crystallisation or reprecipitation and it was characterised by hydrolysis to the 4-carboxylic acid (below).

(*A*) If the solution was acidified (5N-hydrochloric acid) at this point, *ethyl 6-ethoxycarbonyl-2-mercapto-5-nitro-4-pyrimidylaminoacetate* (II; X = SH) (4·5 g.) was precipitated. It crystallised from carbon tetrachloride as yellow prisms, m. p. 127—128° (Found: C, 39·8; H, 4·1. $C_{11}H_{14}O_6N_4S$ requires C, 40·0; H, 4·3%).

2-Substituted 7,8-Dihydro-6-hydroxypteridine-4-carboxylic Acids (V; R = H).—The corresponding ethyl esters (above) were hydrolysed with 2N-sodium hydroxide for 2 min., then cooled as necessary and acidified with dilute hydrochloric acid. The carboxylic acids were purified by repeated precipitation from sodium hydroxide solution or from a solution of a monosodium salt which had been crystallised from water.

Although no undue difficulty had been experienced with the corresponding esters, the carboxylic acids tended to be difficult to burn and held water strongly even when dried over phosphoric oxide *in vacuo* at 150° for 4 hr. The structures of hydrates of 2- and 6-hydroxypteridine and some of their derivatives have been discussed in detail.[13]

2-Substituted 7,8-dihydro-6-hydroxypteridine-4-carboxylic acids (V).

			Found, %			Reqd., %			
X	Decomp.	Formula	C	H	N	C	H	N	Remarks
Cl	>220°	$C_7H_5O_3N_4Cl$	37·1	2·3		36·8	2·2		Dried at 100°
NH_2	>260	$C_7H_7O_3N_5,H_2O$	37·0	4·1		37·0	4·0		Monohydrate after being dried at 150°
			36·8	3·9					
NMe_2	>240	$C_9H_{11}O_3N_5,H_2O$	42·9	5·0		42·4	5·1		Air dried
	>240	$C_9H_{11}O_3N_5,\frac{1}{2}H_2O$	43·9	4·8		43·9	4·9		Dried at 150°
			44·1	4·7					
OH	>250	$C_7H_6O_4N_4$	39·4	3·0	26·2	40·0	2·9	26·7	Dried at 150°
OEt	>220	$C_9H_{10}O_4N_4,5H_2O$	32·2	5·9		32·9	6·1		Air dried
	>220	$C_9H_{10}O_4N_4,\frac{1}{2}H_2O$	43·8	4·3		43·7	4·5		Dried at 150°
SH	>275	$C_7H_6O_3N_4S$	36·8	2·8		37·2	2·7		Dried at 100°
	>280	$C_7H_5O_3N_4SNa,H_2O$	31·8	2·8	21·1	31·6	2·7	21·0	Monosodium salt

Aqueous solutions of these acids generally exhibited a blue or purple fluorescence in ultraviolet light. This was less pronounced than that of the uncyclised amines, being imperceptible in daylight. The mercapto- (V; X = SH, R = H) and dimethylamino- (V; X = NMe_2, R = H) derivatives were exceptional; the former was non-fluorescent while the latter was fluorescent only as its mono- and di-sodium salts.

The authors thank the Governors of the Royal Technical College, Salford, for the award (to A. J. L.) of a College Demonstratorship.

THE ROYAL TECHNICAL COLLEGE, SALFORD. [*Received, May 11th*, 1959.]

[13] Brown and Mason, *J.*, 1956, 3443; Albert, Lister, and Pederson, *J.*, 1956, 4621; Fidler and Wood, *J.*, 1957, 3980.

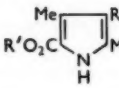
XUM

689. *Colouring Matters Derived from Pyrroles. Part II.* Improved Syntheses of Some Dipyrromethenes and Porphyrins.*

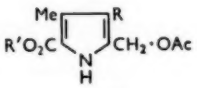
By A. W. Johnson, I. T. Kay, E. Markham, R. Price, and K. B. Shaw.

Esters of 4-substituted 3,5-dimethylpyrrole-2-carboxylic acids, for which an easy synthesis is available, have been used to prepare a variety of dipyrromethanes, dipyrromethenes, and porphyrins. The special properties of the t-butyl and benzyl esters have led to improved methods for the preparation of several dipyrromethenes.

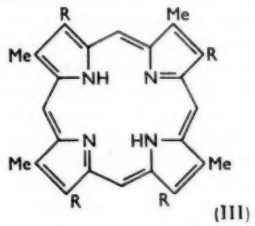
In a previous paper,[1] we described a simple one-stage synthesis of pyrroles of the general structure (I) which made these compounds readily accessible for the preparation of certain porphyrins as well as of dipyrromethane and dipyrromethene intermediates. Some of these reactions are described in the present paper in which emphasis is placed on the special properties of benzyl and t-butyl esters (I; R′ = CH_2Ph or Bu^t) in the pyrrole series.



(I)



(II)



(III)

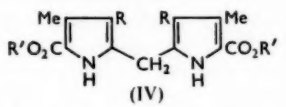
An ester of this type was used as the starting point for a convenient synthesis [2] of the esters of coproporphyrin III (III; R = CH_2·CH_2·CO_2H); the ester (I; R = CH_2·CH_2·CO_2Et, R′ = CH_2Ph) was oxidised with lead tetra-acetate to the 5-acetoxymethyl derivative (II; R = CH_2·CH_2·CO_2Et, R′ = CH_2Ph) and then hydrogenolysed to the corresponding acid (II; R = CH_2·CH_2·CO_2Et, R′ = H). Acid-catalysed polymerisation of this acid gave the coproporphyrin III ester (III; R = CH_2·CH_2·CO_2Et) in 22% yield. By a similar process the acid (II; R = CH_2·CH_2·CO_2Me, R′ = H) has now given coproporphyrin III tetramethyl ester in 29% yield, but the interesting observation has been made that the yield can be increased to 52% if the polymerisation is carried out in the presence of cobaltous chloride, the cobalt complex of the porphyrin being obtained. In an alternative synthesis (cf. ref. 2), coproporphyrin III tetraethyl ester has been obtained directly from the t-butyl ester (II; R = CH_2·CH_2·CO_2Et, R′ = Bu^t) by heating its solution in ethylene glycol under reflux, and ætioporphyrin (probably III; R = Et) has been prepared in 22% yield by a similar method from the t-butyl ester (II; R = Et, R′ = Bu^t). In the latter case the yield of porphyrin (as zinc complex) was appreciably diminished by adding zinc acetate to the reaction mixture. Ætioporphyrin was obtained in one stage from the pyrrole t-butyl ester (I; R = Et, R′ = Bu^t) by heating its solution in acetic acid with one mol. of bromine. Although the yield was low in the single experiment performed, the preparation is nevertheless remarkable in that it represents a two-stage synthesis of ætioporphyrin from aliphatic intermediates. It is presumed that the bromine causes substitution at the α-methyl group, to give an α-bromomethyl derivative which then polymerises in the same manner as the α-acetoxymethyl compound. In this case, addition

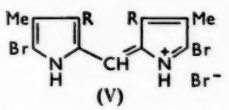
* "A Synthesis of Coproporphyrin III" by Bullock, Johnson, Markham and Shaw (*J.*, 1958, 1430) is taken to be Part I of this series.

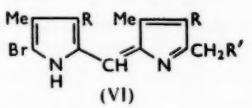
[1] Johnson, Markham, Price, and Shaw, *J.*, 1958, 4254.
[2] Bullock, Johnson, Markham, and Shaw, *J.*, 1958, 1430.

of zinc acetate had no effect on the reaction as the hydrogen bromide formed removed the metal from the porphyrin complex.

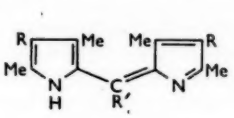
Treatment of the acetoxymethylpyrrole esters (II) with dilute acid gave good yields of the dipyrromethanes (IV; R′ = Et, and R = Me; R′ = CH_2Ph, and R = Et, $CH_2{\cdot}CH_2{\cdot}CO_2Me$, or $CH_2{\cdot}CH_2{\cdot}CO_2Et$). The benzyl esters were readily converted into the corresponding acids (IV; R′ = H) by hydrogenolysis, which causes fewer side reactions than hydrolyses of the ethyl esters. Treatment of the dipyrromethane-5,5′-dicarboxylic acid (IV; R = Et, R′ = H) with bromine in acetic acid [3] gave the 5,5′-dibromodipyrromethene hydrobromide (V; R = Et), and by use of a slightly modified procedure involving bromine in formic acid [4] the analogous compound (V; R = $CH_2{\cdot}CH_2{\cdot}CO_2Et$) was obtained. These 5,5′-dibromodipyrromethenes are useful porphyrin intermediates, *e.g.*, in the synthesis of mesoporphyrin IX.[5]

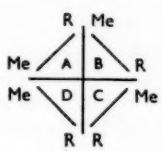

(IV)

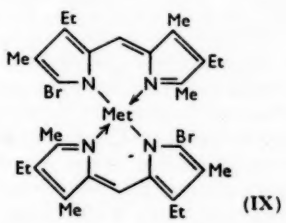

(V)


(VI)

Another important group of dipyrromethenes (VI; R′ = H or Br) which contain an unsymmetrical arrangement of the β-substituents has been prepared in a novel manner by the direct action of bromine on the pyrrole t-butyl ester (I; R = Et, R′ = Bu^t). The mixed products (VI; R′ = H or Br) were separated by extraction with chloroform in which the former, present as a perbromide, was insoluble. Fischer, Baumann, and Riedl [6] had obtained the same mixture of dipyrromethenes (VI; R = Et, R′ = H or Br) by bromination of cryptopyrrole, but the present method avoids the preparation of the unstable cryptopyrrole and thus eliminates at least one preparative stage. In another example of this type of synthesis the pyrrole ester (I; R = CO_2Et, R′ = Bu^t) was converted by bromine into the dipyrromethene (VI; R = CO_2Et, R′ = H).[7]


(VII)


(VIII)


(IX)

A synthesis [8] of symmetrical dipyrromethenes (VII; R′ = H) containing 5,5′-dimethyl groups involves the action of formic and hydrobromic acid on the 2-ethoxycarbonylpyrroles (I; R = Me, Et, or $CH_2{\cdot}CH_2{\cdot}CO_2Et$, R′ = Et), although in the case of the product from the pyrrole containing the β-propionic ester side-chain, some hydrolysis of the ester groups occurred and re-esterification was necessary. Acetic acid cannot replace formic acid for the preparation of *meso*-methyl analogues of (VIII; R′ = Me), but it has now been found that these compounds can be obtained easily from the 2-t-butoxycarbonylpyrroles (I; R = Me or $CH_2{\cdot}CH_2{\cdot}CO_2Me$, R′ = Bu^t) by the action of acetyl chloride in acetic acid. It is, of course, necessary that the intermediate pyrrole-2-carboxylic acids in these reactions should be decarboxylated readily; the pyrrole (I; R = CO_2Et, R′ = Bu^t)

[3] Fischer, Halbig, and Walach, *Annalen*, 1927, **452**, 268.
[4] Cf. MacDonald and Michl, *Canad. J. Chem.*, 1956, **34**, 1768.
[5] Fischer and Stangler, *Annalen*, 1928, **462**, 251.
[6] Fischer, Bauman, and Riedl, *ibid.*, 1929, **475**, 205.
[7] Fischer and Bäumler, *ibid.*, 1929, **468**, 58.
[8] Fischer *et al.*, *ibid.*, 1928, **466**, 147; 1930, **483**, 251; 1932, **492**, 128.

XUM

merely formed the corresponding monocarboxylic acid after reaction with acetyl chloride. As in the brominative decarboxylation described above, this synthesis of dipyrromethenes avoids the preparation of trialkylpyrroles.

In considering dipyrromethene intermediates for the synthesis of III-type porphyrins, abbreviated as (VIII) where only the β-pyrrole substituents are indicated, the union to be effected can be either AB ⟶ CD or AD ⟶ BC, where AB is the same as BC. The preparation, from the pyrroles (I), of all three types of dipyrromethene required for these syntheses has now been described: (V) corresponds to CD, (VI) to AB or BC, and (VII) to AD. There remains, of course, the problem of having the necessary α-substituents present on the dipyrromethenes in order to form the remaining *meso*-carbons of the porphyrin.

Although metal salts are frequently added to the reaction mixtures in syntheses of phthalocyanins and benzoporphyrins,[9] it is usual to employ the free dipyrromethenes in the preparation of the porphyrins themselves. After it had been observed that the action of palladium–strontium carbonate on 5-bromo-5′-bromomethyl-3,4′-diethyl-4,3′-dimethyldipyrromethene hydrobromide (VI; R = Et, R′ = Br) in ethanolic solution gave the palladium complex of ætioporphyrin I (without the metal the reaction can be effected by formic acid [10]), it was decided to assess the effect of different metals in this type of synthesis.[11] The dipyrromethene used was 5-bromo-3,4′-diethyl-4,5,3′-trimethyldipyrromethene and the cobalt, nickel, copper, and zinc derivatives (IX) were prepared by standard methods. Solutions of the metal complexes were not affected by aqueous potassium hydroxide, but the metal was rapidly and quantitatively removed by treatment with aqueous potassium cyanide. Each of these metal complexes as well as the free dipyrromethene was heated under reflux in *o*-dichlorobenzene for 60 min. and the amount of porphyrin (either the metal derivative or the free base) was estimated spectroscopically. Yields were as follows: cobalt, 17%; zinc, 15%; nickel, 14%; copper, 7%; and free base, 11%. It is clear that the presence of the metal results only in a modest increase of yield under these conditions. A determination of the magnetic susceptibility ($\mu_{eff.}$ = 4·5) of the green cobalt complex of (VII; R = Et, R′ = H), kindly carried out by Professor R. Nyholm and Mr. D. J. Machin, indicated that it was tetrahedral and all of the above metal complexes are probably of this type. There is thus an appreciable energy barrier to be overcome before the rearrangement to the planar metalloporphyrin can take place and this approach would not appear to offer any advantage over the conventional methods, *e.g.*, heating the dipyrromethene hydrobromide in succinic acid. In another attempt to utilise the dipyrromethene–metal complexes, the possibility of preparing a mixed metal complex from two dipyrromethenes was examined in order to assess the possibility of preparing porphyrins of the mesoporphyrin IX type. This approach would be of practical value if the mixture of symmetrical and unsymmetrical metallo-dipyrromethenes was more easily separated than the mixed porphyrins. Equimolecular quantities of 3,3′,4,4′,5,5′-hexamethyldipyrromethene and 4,4′-diethyl-3,3′,5,5′-tetramethyldipyrromethene were treated with cobalt acetate, and the resulting mixture was separated by solvent-extraction and crystallisation. An *X*-ray powder photograph of the mixed cobalt complex, taken by Dr. R. B. Elliott of the Geology Department, University of Nottingham, confirmed that it differed from both of the symmetrical cobalt complexes. In other cases, however, the mixed dipyrromethene–metal complex could not be isolated conveniently and this approach has consequently been abandoned.

Experimental

Preparation of Pyrrole Intermediates.

t-Butyl 4-Ethyl-3,5-dimethylpyrrole-2-carboxylate (I; R = Et, R′ = Bu^t).—Redistilled t-butyl acetoacetate (260 g.) in glacial acetic acid (300 c.c.) was treated with aqueous sodium

[9] Linstead and Weiss, *J.*, 1950, 2975.
[10] Fischer and Klarer, *Annalen*, 1926, **450**, 181.
[11] Corwin and Sydow, *J. Amer. Chem. Soc.*, 1953, **75**, 4484.

nitrite (135 g. in 300 c.c.) with stirring during 75 min. at 10—12° (ice-cooling). The product was kept for a further hr. at 4°, then overnight at room temperature. The following day, 3-ethylpentane-2,4-dione [1] (210 g.) and acetic acid (60 c.c.) were added with stirring, followed by zinc dust (210 g.) at such a rate as to keep the temperature at 80—85°. Next, the mixture was stirred for a further 30 min., then heated at 100° for 2 hr. The hot solution was poured, with stirring, into cold water (5 l.), and the precipitated solid was separated and dissolved in hot ethanol (500 c.c.). The clarified solution was diluted with water to produce a faint turbidity and then kept, the *ester* being obtained as colourless needles (118 g., 31%, m. p. 134—135°) (Found: C, 69·6; H, 9·8; N, 6·3. $C_{13}H_{21}O_2N$ requires C, 69·9; H, 9·5; N, 6·3%).

t-Butyl 3-2′-Methoxycarbonylethyl-2,4-dimethylpyrrole-2-carboxylate (I; R = $CH_2{\cdot}CH_2{\cdot}CO_2Me$, R′ = Bu^t).—Prepared in a similar manner from t-butyl acetoacetate and methyl 4-acetyl-5-oxohexanoate,[1] this *ester* (35%) formed colourless needles, m. p. 99—100° (Found: C, 64·0; H, 8·2; N, 5·15. $C_{18}H_{23}O_4N$ requires C, 63·8; H, 7·8; N, 5·0%).

A similar reaction between t-butyl acetoacetate and ethyl 4-acetyl-5-oxohexanoate gave *t-butyl 3-2′-ethoxycarbonylethyl-2,4-dimethylpyrrole-2-carboxylate* (I; R = $CH_2{\cdot}CH_2{\cdot}CO_2Et$, R′ = Bu^t) as colourless needles (37%), m. p. 69° (Found: C, 65·3; H, 8·3; N, 5·0. $C_{16}H_{25}O_4N$ requires C, 65·05; H, 8·5; N, 4·75%).

Ethyl 5-Acetoxymethyl-3,4-dimethylpyrrole-2-carboxylate (II; R = Me, R′ = Et).—Lead tetra-acetate (24·5 g.) was added to a solution of ethyl 2,3,4-trimethylpyrrole-5-carboxylate [2] (10 g.) in glacial acetic acid (250 c.c.) at room temperature during 15 min. with stirring. Stirring was continued for a further 2 hr., after which most of the solvent was removed under reduced pressure, and the residue poured into water (500 c.c.). The precipitated solid was separated, washed with water, and crystallised from aqueous acetone, forming colourless needles, m. p. 131—132° (lit.,[12] 132°) (11·5 g., 87%).

Benzyl 5-Acetoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate (II; R = Et, R′ = CH_2Ph).—Obtained (19 g., 66%) from benzyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate [1] (24·5 g.) by a similar process, and after crystallisation from acetone, this *compound* formed colourless needles, m. p. 122° (Found: C, 68·7; H, 6·75; N, 4·7. $C_{18}H_{21}O_4N$ requires C, 68·55; H, 6·7; N, 4·45%).

Benzyl 5-Acetoxymethyl-4-2′-methoxycarbonylethyl-3-methylpyrrole-2-carboxylate (II; R = $CH_2{\cdot}CH_2{\cdot}CO_2Me$, R′ = CH_2Ph).—This *diester* was obtained from benzyl 4-2′-methoxycarbonylethyl-3,5-dimethylpyrrole-2-carboxylate [1] in 69% yield by a similar process. It formed colourless needles, m. p. 111—112°, from aqueous acetone (Found: C, 64·2; H, 6·2; N, 3·7. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N, 3·75%).

t-Butyl 5-Acetoxymethyl-4-2′-ethoxycarbonylethyl-3-methylpyrrole-2-carboxylate (II; R = $CH_2{\cdot}CH_2{\cdot}CO_2Et$, R′ = Bu^t).—Prepared (50%) likewise from t-butyl 4,2′-ethoxycarbonylethyl-3,5-dimethylpyrrole-2-carboxylate (above) with lead tetra-acetate, this *butyl derivative* formed colourless needles, m. p. 84—85° (Found: C, 61·3; H, 7·4; N, 4·3. $C_{18}H_{27}O_6N$ requires C, 61·2; H, 7·7; N, 3·95%).

Preparation of Dipyrromethanes.

Diethyl 3,3′,4,4′-Tetramethyldipyrromethane-5,5′-dicarboxylate (IV; R = Me, R′ = Et).—Ethyl 5-acetoxymethyl-3,4-dimethylpyrrole-2-carboxylate (7 g.) was dissolved in ethanol (200 c.c.) containing concentrated hydrochloric acid (5 c.c.) and heated under reflux for 1 hr. On cooling, the product crystallised. When separated, washed with ethanol, and dried, it had m. p. 196—198° (lit.,[13] 198°), unchanged after recrystallisation from ethanol.

Dibenzyl 3,3′-Diethyl-4,4′-dimethyldipyrromethane-5,5′-dicarboxylate (IV; R = Et, R′ = CH_2Ph).—Prepared (66%) similarly from benzyl 5-acetoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate, this *analogue* formed colourless needles (from ethanol), m. p. 126—127° (Found: C, 74·5; H, 6·75; N, 5·8. $C_{31}H_{34}O_4N_2$ requires C, 74·65; H, 6·85; N, 5·6%).

Dibenzyl 3,3′-di-(2-ethoxycarbonylethyl)-4,4′-dimethyldipyrromethane-5,5′-dicarboxylate (IV; R = $\cdot CH_2{\cdot}CH_2{\cdot}CO_2Et$; R′ = CH_2Ph), prepared (72%) in a similar manner from benzyl 5-acetoxymethyl-4-2′-ethoxycarbonylethyl-3-methylpyrrole-2-carboxylate,[2] formed colourless needles (from ethanol), m. p. 102—103° (Found: C, 69·1; H, 6·5; N, 4·65. $C_{37}H_{42}O_8N_2$ requires C, 69·15; H, 6·6; N, 4·35%).

Dibenzyl 3,3′-Di-(2-methoxycarbonylethyl)-4,4′-dimethyldipyrromethane-5,5′-dicarboxylate (IV;

[12] Siedel and Winkler, *Annalen*, 1943, **554**, 162.
[13] Fischer and Walach, *ibid.*, 1926, **450**, 109.

XUM

R = CH_2·CH_2·CO_2Me, R′ = CH_2Ph).—(i) Prepared similarly (65%) from benzyl 5-acetoxymethyl-4,2′-methoxycarbonylethyl-3-methylpyrrole-2-carboxylate, this *dipyrromethane* formed colourless needles, m. p. 96—97°, from ethanol (Found: C, 68·2; H, 6·0; N, 4·85. $C_{35}H_{38}O_8N_2$ requires C, 68·4; H, 6·25; N, 4·55%).

(ii) The same acetoxy-pyrrole (1 g.) was dissolved in methanol (30 c.c.) containing concentrated hydrochloric acid (3 drops) and kept at room temperature for one month. The solution was reduced to 10 c.c., and the resulting colourless solid separated and crystallised from ethanol; it was obtained as colourless needles, m. p. alone and mixed with the product from the previous experiment, 96—97°.

Preparation of Dipyrromethenes.

5,5′-Dibromo-3,3′-diethyl-4,4′-dimethyldipyrromethene (V; R = Et).—Dibenzyl 3,3′-diethyl-4,4′-dimethyldipyrromethane-5,5′-dicarboxylate (above; 9·1 g.) was dissolved in methanol (100 c.c.), and methanol-washed Raney nickel (5 g.) was added. The mixture was hydrogenated at 100—110°/140 atm. for 2 hr., after which the catalyst and solvent were removed. The residual oil was treated in glacial acetic acid (40 c.c.) with bromine (3·0 c.c.) in glacial acetic acid (10 c.c.) for 2 hr. at room temperature. The precipitated hydrobromide was separated, washed with light petroleum, and dried (5·7 g., 67%). The free base was prepared by treating a methanolic solution of the hydrobromide with ammonia. It crystallised from methanol in yellow needles, m. p. 181—182° (lit.,[3] 184°) (Found: C, 46·35; H, 4·5; N, 7·1. Calc. for $C_{15}H_{18}N_2Br_2$: C, 46·65; H, 4·7; N, 7·25%), $\lambda_{max.}$ 325, 491 mμ (log ε 3·56, 4·5).* The *cobalt complex* was prepared by treating the hydrobromide (1 g.) in ethanol (50 c.c.) and aqueous ammonia (0·5 c.c.; *d* 0·88) with a saturated solution (2·5 c.c.) of cobalt acetate in aqueous ammonia. After removal of the solvent, the residue was dissolved in chloroform, washed several times with water, and dried ($MgSO_4$). The solvent was removed and the cobalt complex (800 mg.) crystallised as green needles from chloroform–methanol (Found: C, 43·3; H, 4·1; N, 6·85. $C_{30}H_{34}N_4Br_4Co$ requires C, 43·45; H, 4·15; N, 6·75%), $\lambda_{max.}$ at 239, 319, 377, 515, 710, and 770 mμ (log ε 4·42, 3·8; 4·86, 3·6, 2·8 and 2·91) with an inflection at 585 mμ (log ε 3·55).

5,5′-Dibromo-3,3′-di-(2-ethoxycarbonylethyl)-4,4′-dimethyldipyrromethene (V; R = CH_2·CH_2·CO_2Et).—Dibenzyl 3,3′-di-(2-ethoxycarbonylethyl)-4,4′-dimethyldipyrromethane-5,5′-dicarboxylate (above; 3 g.) was hydrogenated in methanol (150 c.c.) over Adams catalyst. The solvent was then removed under reduced pressure and the resulting off-white solid, decomp. >160°, washed with ether, dried (2·0 g., 80%), and treated with bromine (3 c.c.) in 90% formic acid (15 c.c.). The mixture was kept for 1 hr. before being left overnight in a desiccator over solid sodium hydroxide at *ca.* 30 mm. The product was separated, washed with formic acid, and dried (yield 3 g., 75%). The *hydrobromide* crystallised from ethanol as violet needles, m. p. 188—189° (Found: C, 41·7; H, 4·35; N, 4·25. $C_{21}H_{27}O_4N_2Br_3$ requires C, 41·3; H, 4·45; N, 4·55%), $\lambda_{max.}$ 455 mμ (log ε 4·46).

The hydrobromide (2·4 g.) was dissolved in methanol (50 c.c.), and the solution made alkaline with dilute ammonia. The precipitated orange *base* was separated, washed with water, dried (1·9 g., 90%), and crystallised from ethanol, forming orange needles, m. p. 92—94° (Found: N, 5·4. $C_{21}H_{26}O_4N_2Br_2$ requires N, 5·3%). The *cobalt complex* crystallised from chloroform–methanol in green needles, m. p. 175—176° (Found: C, 45·2; H, 4·4; N, 5·3. $C_{42}H_{50}O_8N_4Br_4Co$ requires C, 45·15; H, 4·5; N, 5·0%). The *nickel complex* crystallised from chloroform–methanol in olive-green needles, m. p. 178—179° (Found: C, 44·8; H, 3·90; N, 5·15. $C_{42}H_{50}O_8N_4Br_4Ni$ requires C, 45·15; H, 4·48; N, 5·0%).

5-Bromo-5′-bromomethyl-3,4′-diethyl-4,3′-dimethyldipyrromethene Hydrobromide (VI; R = Et, R′ = Br).—t-Butyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (36 g.) in glacial acetic acid (250 c.c.) was treated with bromine (20 c.c.) in glacial acetic acid (100 c.c.). After the vigorous reaction had subsided, the mixture was kept for 1 hr. and the steel-blue crystals (18 g.) were separated and washed with light petroleum (b. p. 60—80°). The mixed product (5 g.) was separated by extraction with chloroform at <40°, the above dipyrromethene hydrobromide[6] being obtained from the extract as red prisms (3 g.), m. p. >350° (Found: C, 39·8; H, 4·4; N, 5·6. Calc. for $C_{16}H_{21}N_2Br_3$: C, 39·9; H, 4·4; N, 5·8%).

5-Bromo-3,4′-diethyl-4,3′,5′-trimethyldipyrromethene Hydrobromide Perbromide (as VI; R = Et, R′ = H).—The chloroform-insoluble fraction from the above separation was obtained as a brick-red powder (1·4 g.), m. p. 147° (lit.,[6] 149°), which was the above-named perbromide.

* Absorption maxima are for chloroform solution, throughout.

Metal complexes. (i) The methene hydrobromide perbromide (3 g.) was dissolved in ethanol (15 c.c.) containing aqueous ammonia (2·5 c.c.; *d* 0·88), and a saturated solution of cobaltous acetate in aqueous ammonia (10 c.c.) was added. The mixture was boiled gently for 5 min., then cooled, and water (100 c.c.) was added. The solution was extracted with chloroform (3 × 25 c.c.), and the combined extracts were washed and dried. After concentration of the chloroform solution to 10 c.c., crystallisation was induced by gradual addition of methanol. The *cobalt complex* so obtained formed green plates, m. p. 174° (Found: C, 54·8; H, 6·0; N, 8·0. $C_{32}H_{40}N_4Br_2Co$ requires C, 54·9; H, 5·8; N, 8·0%), $\lambda_{max.}$ 376, 509, 705 and 765 mμ (log ε 4·25, 5·14, 2·66, and 2·72, respectively) with inflections at 400 and 615 mμ (log ε 4·14 and 3·51). (ii) Prepared in an analogous manner by using ammoniacal nickel chloride, the *nickel complex* (850 mg.) formed olive-green needles, m. p. 174° (Found: C, 54·9; H, 5·9; N, 7·6. $C_{32}H_{40}N_4Br_2Ni$ requires C, 54·95; H, 5·8; N, 8·0%). (iii) Prepared similarly by using ammoniacal cupric acetate, the *copper complex* (1 g.) formed green prisms, m. p. 156°, which could not be recrystallised satisfactorily (Found: N, 7·95. Calc. for $C_{32}H_{40}N_4Br_2Cu$: N, 7·25%), $\lambda_{max.}$ at 338, 397, 491, and 800 mμ (log ε 4·03, 4·14, 4·69, and 3·51 respectively) with inflections at 380 and 520 mμ (log ε 4·12 and 4·29). (iv) Prepared similarly by using ethanolic zinc acetate, the *zinc complex* (900 mg.), m. p. 177°, formed brown needles with a golden metallic sheen (Found: C, 54·6; H, 5·55; N, 8·05. $C_{32}H_{40}N_4Br_2Zn$ requires C, 54·45; H, 5·7; N, 7·95%), $\lambda_{max.}$ at 233, 291, 365, and 507 mμ (log ε 4·29, 3·75, 4·01, and 5·06) with inflections at 310 and 480 mμ (log ε 3·67 and 4·82).

These metal complexes (100 mg.) were all converted into the metal derivatives of ætioporphyrin I by suspending them in *o*-dichlorobenzene (2 c.c.), raising the temperature of the suspension to the b. p. during ½ hr., then heating the solutions under reflux for 1 hr. A similar reaction was carried out with the free base. After cooling, chloroform (5 c.c.) was added to each mixture, which was chromatographed on alumina (Spence type H; 30 × 2·5 cm.). The porphyrin band was eluted (hand spectroscope), and the eluate made up to 100 c.c. An aliquot part was diluted (1 : 5) and examined spectroscopically over the range 350—430 mμ. The yields of metal porphyrin were calculated from the intensity of the strong band near 400 mμ, after measurement of the intensity of absorption of each of the porphyrin derivatives: ætioporphyrin I, log ε 5·23 at 396 mμ; cobalt complex log ε 5·35 at 393 mμ; nickel complex, log ε 5·26 at 392 mμ; copper complex, log ε 5·59 at 398 mμ; zinc complex, log ε 5·43 at 402 mμ. On this basis the percentage conversions were: cobalt, 17%; nickel, 14%; copper, 7%; zinc, 15%; free base, 11%.

5-Bromo-3,4'-di(ethoxycarbonyl)-4,3',5'-trimethyldipyrromethene (VI; R = CO_2Et, R' = H).—t-Butyl 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-carboxylate [1] (2·59 g.) was suspended in glacial acetic acid (5 c.c.), and bromine (0·9 c.c.) in acetic acid (10 c.c.) was added. The mixture was kept for 15 min. with occasional stirring, then the hydrobromide (1·65 g.) was separated and washed with light petroleum. It crystallised from chloroform–light petroleum as brick-red felted needles which decomposed before melting [$\lambda_{max.}$ 295 mμ (log ε 3·63)].

The hydrobromide (1·5 g.) was suspended in methanol (50 c.c.), and aqueous ammonia (5 c.c.; *d* 0·88) was added. The mixture was boiled gently for 5 min., then cooled, the free base (1·1 g.) separating. It crystallised from acetone as brown needles with a golden reflex, m. p. 151° (lit.,[7] 153°) (Found: N, 5·4. Calc. for $C_{18}H_{21}O_4N_2Br$: N, 5·65%).

The *cobalt complex* (750 mg.) from this base (1 g.) formed green needles, m. p. 233° (Found: C, 49·8; H, 4·8; N, 6·1. $C_{36}H_{40}O_8N_4Br_2Co$ requires C, 49·5; H, 4·6; N, 6·4%), $\lambda_{max.}$ 376 and 522 mμ (log ε 3·08 and 5·11).

3,3',4,4',5,5'-Hexamethyldipyrromethene (VII; R = Me, R' = H).—Ethyl 3,4,5-trimethylpyrrole-2-carboxylate [2] (3·62 g.) was dissolved in hot 90% formic acid (5 c.c.), and 48% hydrobromic acid (4 c.c.) was added. The mixture was heated on the steam-bath for 3 hr., then cooled. The product (2·55 g., 83%) was separated and washed with water, methanol, and ether. The *hydrobromide* crystallised from a hot solution in chloroform–light petroleum (b. p. 60—80°; 3 : 1) as dark red prisms with a metallic sheen, m. p. 294—295° (Found: C, 58·3; H, 6·8; N, 9·1. $C_{15}H_{21}N_2Br$ requires C, 58·4; H, 6·95; N, 8·9%), $\lambda_{max.}$ 288, 363, and 487 mμ (log ε 3·12, 3·81, and 4·99). The hydrobromide (5 g.) was dissolved in chloroform (500 c.c.) and shaken with aqueous ammonia (equal vols. of water and *d* 0·88). The chloroform layer was separated and dried, and after removal of the solvent the residue was crystallised from ethanol. The free base (4 g.) was thus obtained as red prisms, m. p. 168° (decomp.) (lit.,[13] 172°) (Found: C, 78·9; H, 8·8; N, 12·3. Calc. for $C_{15}H_{20}N_2$: C, 78·9; H, 8·75; N, 12·3%), $\lambda_{max.}$ 326 and 445 mμ

(log ε 3·52 and 4·46). The cobalt complex [6] formed green needles from chloroform–methanol. It sublimed at >330° (Found: C, 70·3; H, 7·45; N, 10·6. Calc. for $C_{30}H_{38}N_4Co$: C, 70·2; H, 7·5; N, 10·9%) and had $\lambda_{max.}$ 375, 507, 610, 710, and 765 mμ (log ε 4·21, 5·12, 3·48, 2·62, and 2·71 respectively) with an inflection at 563 mμ (log ε 3·62).

4,4-Diethyl-3,3′,5,5′-tetramethyldipyrromethene (VII; R = Et, R′ = H) *Derivatives.*—By reaction with formic and hydrobromic acid as described in the foregoing experiment, ethyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate was converted into *4,4′-diethyl-3,3′,5,5′-tetramethyldipyrromethene hydrobromide* (88%), m. p. 230—246° (decomp.) (Found: C, 60·6; H, 7·3; N, 8·35. $C_{17}H_{25}N_2Br$ requires C, 60·55; H, 7·45; N, 8·3%), $\lambda_{max.}$ 288, 364, and 488 mμ (log ε 3·14, 3·85, and 5·00 respectively).

The hydrobromide (1 g.) was dissolved in ethanol (50 c.c.) containing aqueous ammonia (1 c.c.; *d* 0·88), and to this a saturated solution (10 c.c.) of cobalt acetate in ammonia (*d* 0·88) was added. The cobalt complex which separated crystallised as green prisms (950 mg.), m. p. 198° (lit.,[3] 198°), from ethanol (Found: C, 71·4; H, 7·8; N, 10·3. Calc. for $C_{34}H_{46}N_4Co$: C, 71·7; H, 8·14; N, 10·15%); it had $\lambda_{max.}$ 373, 509, 710, and 770 mμ (log ε 4·22, 5·08, 2·66, and 2·70) with an inflection at 615 mμ (log ε 3·47).

The Mixed Cobalt Complex of 3,3′,4,4′,5,5′-Hexamethyl- and 4,4′-Diethyl-3,3′,5,5′-tetramethyldipyrromethene.—A saturated solution of cobalt acetate in aqueous ammonia (20 c.c.; *d* 0·88) was added to a solution of the hexamethyldipyrromethene hydrobromide (1·45 g.) and the diethyltetramethyldipyrromethene hydrobromide (1·58 g.) in hot ethanol (50 c.c.) containing aqueous ammonia (3 c.c.; *d* 0·88). The solution was boiled gently for 5 min. and cooled. A mixture of cobalt complexes (2·4 g.) separated. Extraction (thimble) of the mixture with hot ethanol gave the cobalt complex of 4,4′-diethyl-3,3′,5,5′-tetramethyldipyrromethene (490 mg.) which, after crystallisation from chloroform–methanol, had m. p. 198°, not depressed on admixture with the product from the previous experiment (Found: C, 71·8; H, 8·2; N, 10·0%).

The residue (1·5 g.) in the thimble was further extracted with hot light petroleum (b. p. 60—80°) and yielded green crystals (540 mg.) which sublimed at 240—260°, and were crystallised from chloroform–methanol. This was the mixed *complex* (Found: C, 70·8; H, 7·85; N, 10·0, 10·1. $C_{32}H_{42}N_4Co$ requires C, 70·95; H, 7·65; N, 10·35%), $\lambda_{max.}$ 375, 508, 615, 710, and 770 mμ (log ε 4·28, 5·21, 3·54, 2·66, and 2·77 respectively) with an inflection at 570 mμ (log ε 3·70). *X*-Ray powder diagrams showed that the 3 cobalt complexes differed from each other. The residue (0·8 g.) still remaining in the thimble was extracted with chloroform–methanol (1 : 1); then concentration of the extract gave the cobalt complex of hexamethyldipyrromethene as green needles which sublimed at >330°. It was recrystallised from chloroform–methanol (Found: C, 69·9; H, 7·6; N, 10·8%).

4,4′-Di-(2-ethoxycarbonylethyl)-3,3′,5,5′-tetramethyldipyrromethene (VII; R = CH_2·CH_2·CO_2Et, R′ = H).—Ethyl 4-2′-ethoxycarbonylethyl-3,5-dimethylpyrrole-2-carboxylate [2] (22·5 g.) was heated on the water-bath with formic acid (21 c.c.) and concentrated hydrochloric acid (21 c.c.) until effervescence ceased (*ca.* 2 hr.). The solution was cooled (ice-bath), and the dark red crystals (13·7 g.) were separated, washed with ether, and dried. The crude product (8 g.) was dissolved in dry ethanol (75 c.c.), cooled (ice), and saturated with dry hydrogen chloride. Next day, the solution was reduced to *ca.* 50 c.c. and cooled, and the dark red crystalline *hydrochloride* was separated and dried (7 g.). After crystallisation from ethanol it had m. p. 184—186° (Found: C, 63·9; H, 7·35; N, 6·1. $C_{23}H_{33}O_4N_2Cl$ requires C, 63·2; H, 7·6; N, 6·4%), $\lambda_{max.}$ 288, 360, and 484 mμ (log ε 3·10, 3·77, and 5·07 respectively). The corresponding free base, obtained from a chloroform solution of the hydrochloride by shaking with aqueous ammonia gave a *cobalt complex* which formed green needles, m. p. 137—138°, from ethanol (Found: C, 64·0; H, 7·2; N, 6·5. $C_{46}H_{62}O_8N_4Co$ requires C, 64·4; H, 7·3; N, 6·55%), having $\lambda_{max.}$ 374, 505, 610, 705, and 760 mμ (log ε 4·2, 5·19, 3·49, 2·63, and 2·71 respectively).

Zinc Complex of 3,3′,4,4′,5,5′,α-Heptamethyldipyrromethene (VII; R = R′ = Me).—t-Butyl 3,4,5-trimethylpyrrole-2-carboxylate [2] (2·09 g.) was mixed with acetyl chloride (2 c.c.) and glacial acetic acid (2 c.c.) and heated under reflux for 1·5 hr. The solution was cooled, diluted with water (250 c.c.), and neutralised with aqueous ammonia. The yellow solid thus obtained was separated, washed with water, and dried. The crude dipyrromethene (2·05 g.) was unstable and could not be crystallised. It (1 g.) was dissolved in warm ethanol (25 c.c.), and a saturated solution of zinc acetate in ethanol (10 c.c.) containing one drop of aqueous ammonia was added. The mixture was warmed for 5 min. and then cooled, the zinc complex (400 mg.) separating as

orange needles with a green metallic sheen. A further quantity of the complex was obtained by adding more zinc acetate solution to the filtrate. The *zinc complex*, crystallised from chloroform–methanol, had m. p. 288° after sintering at 260° (Found: C, 70·5; H, 7·8; N, 10·0. $C_{32}H_{42}N_4Zn$ requires C, 70·1; H, 7·7; N, 10·2%), $\lambda_{max.}$ 305, 367, and 505 mμ (log ε 3·91, 3·91, and 4·06 respectively).

Zinc Complex of 4,4′-Di-(2-methoxycarbonylethyl)-3,3′,5,5′,α-pentamethyldipyrromethene (VII; R = CH_2·CH_2·CO_2Me, R′ = Me).—Prepared from t-butyl 4-2′-methoxycarbonylethyl-3,5-dimethylpyrrole-2-carboxylate (above; 2 g.) in a similar manner, the free dipyrromethene (1·4 g.) was again unstable and was characterised as the bright orange *zinc complex* (0·7 g.) (from chloroform–methanol), m. p. 218° (decomp.) (Found: C, 62·9; H, 7·05; N, 6·75. $C_{44}H_{58}O_8N_4Zn$ requires C, 63·15; H, 7·0; N, 6·7%), $\lambda_{max.}$ 235, 304, 365, and 501 mμ (log ε 4·32, 3·89, 3·84, and 5·05 respectively).

A similar reaction with t-butyl 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-carboxylate [1] gave only the corresponding acid, 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-carboxylic acid [14] as colourless needles, m. p. 196° [lit., 202° (decomp.)] (from ethanol) (Found: C, 57·0; H, 5·8. Calc. for $C_{10}H_{13}O_4N$: C, 56·9; H, 6·2%).

Preparation of Porphyrins

Coproporphyrin III Tetramethyl Ester (III; R = CH_2·CH_2·CO_2Me).—This was prepared from benzyl 5-acetoxymethyl-4-2′-methoxycarbonylethyl-3-methylpyrrole-2-carboxylate by hydrogenolysis to the free acid and then polymerisation by acetic acid and methanol as described earlier.[2] The product (29%) crystallised from chloroform–methanol in red-brown needles, m. p. 151—154°. This compound has been reported to exist in dimorphic forms, and m. p.s over a wide range have been quoted for each of these, *e.g.*, lower-melting, 135°,[15] 145—146°,[16] 155—157°,[17] and higher-melting, 165°,[18] 170°,[16] 181—182°.[17] The higher-melting form was not observed in this experiment. Light absorption max. were at 400, 497, 531, 566, and 620 mμ (log ε 5·19, 4·10, 3·93, 3·76, and 3·62 respectively). The cobalt complex crystallised from chloroform–methanol in red-brown needles, m. p. 194—197°, $\lambda_{max.}$ 267, 327, 413, 520, and 555 mμ (log ε 4·15, 4·24, 5·11, 4·01, and 4·28 respectively).

The cobalt complex was also obtained (52%) by carrying out the polymerisation of 5-acetoxymethyl-4-2′-methoxycarbonylethyl-3-methylpyrrole-2-carboxylic acid (from 2·0 g. of the benzyl ester) in methanol (50 c.c.) containing glacial acetic acid (10 c.c.), the solution being heated under reflux in the presence of cobaltous chloride (4 g.) for 7 hr. The deep red solution so obtained was aerated for *ca.* 12 hr., then diluted with water (100 c.c.), made alkaline with ammonia, and extracted with chloroform (6 × 50 c.c.). The mixed chloroform extracts were dried ($MgSO_4$), reduced in volume, and chromatographed on alumina as before. The solvent was removed from the eluted main band, and the residue crystallised from chloroform–methanol, forming reddish-brown needles, m. p. 195—198° alone and mixed with the previous product (Found: C, 62·4; H, 5·9; N, 7·4. $C_{40}H_{44}O_8N_4Co$ requires C, 62·6; H, 5·8; N, 7·3%). The light absorption was similar to that of the previous product.

Coproporphyrin III Tetraethyl Ester (III; R = CH_2·CH_2·CO_2Et).—t-Butyl 5-acetoxymethyl-4-2′-ethoxycarbonylethyl-3-methylpyrrole-2-carboxylate (1·5 g.) was heated in ethylene glycol (15 c.c.) under reflux for 1 hr., then cooled. Methanol (50 c.c.) was added and the solution aerated for 17 hr. Water (75 c.c.) was then added and the porphyrin extracted with chloroform until the extract showed no porphyrin absorption when viewed in the hand spectroscope. The chloroform extract was dried, concentrated to 20 c.c., and chromatographed on a column (30 × 2 cm.) of alumina. Elution of the product was followed by means of the hand spectroscope and, after removal of the solvent from the eluted porphyrin solution, the residue was crystallised from chloroform–methanol, to give coproporphyrin III tetraethyl ester as reddish-brown needles (150 mg., 19%), m. p. 146—148° (lit.,[2] 147—149°), $\lambda_{max.}$ 266, 401, 499, 534, 569, and 620 mμ (log ε 3·92, 5·28, 4·15, 3·99, 3·82, and 3·64 respectively).

Ætioporphyrin III (III; R = Et).—(i) t-Butyl 5-acetoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate (above; 1·0 g.) was suspended in ethylene glycol (10 c.c.) and heated under reflux

[14] Knorr, *Annalen.*, 1886, **236**, 290.
[15] Fischer and Andersag, *ibid.*, 1927, **458**, 117.
[16] Fischer, Platz, and Morgenroth, *Z. physiol. Chem.*, 1929, **182**, 284.
[17] Gray and Holt, *Biochem. J.*, 1948, **43**, 191.
[18] Fischer and Hiernis, *Z. physiol. Chem.*, 1931, **196**, 162.

for 30 min. The dark solution was cooled, diluted with methanol (40 c.c.), and aerated for 8 hr., further methanol being added as required to maintain constant volume. Water (200 c.c.) was added and the solution extracted with chloroform (3 × 20 c.c.). The chloroform extracts were washed with water, dried ($MgSO_4$), concentrated to *ca.* 5 c.c., and chromatographed on alumina (Spence type H; 30 × 1·5 cm.). The porphyrin fraction was collected (hand spectroscope), and, after removal of the solvent, the residue crystallised from chloroform–methanol as purple prisms (99 mg., 22·5%) (Found: C, 80·0; H, 7·75; N, 11·6. Calc. for $C_{32}H_{38}N_4$: C, 80·3; H, 8·0; N, 11·7%), $\lambda_{max.}$ 246, 269, 396, 497, 532, 566, 620, and 645 mμ (log ε 3·90, 3·89, 5·22, 4·13, 3·99, 3·81, 3·65, and 2·62 respectively).

(ii) The pyrrole t-butyl ester (10 g.) of the foregoing experiment was mixed with zinc acetate (2·5 g.), suspended in ethylene glycol (80 c.c.), and heated under reflux for 90 min. After cooling, the mixture was aerated for 5 hr., water (200 c.c.) was added, and the solution thoroughly extracted with chloroform. The combined chloroform extracts were dried and the solvent was removed, leaving a bright green solid (1·8 g.) which was extracted continuously from a thimble with ether (25 c.c.). The residue in the thimble was crystallised twice from chloroform–methanol, as orange-red needles (30 mg.) which showed the typical metal-porphyrin spectrum in chloroform solution. The other products from the reaction have not been identified.

(iii) t-Butyl 3-ethyl-2,4-dimethylpyrrole-5-carboxylate (2 g.) in glacial acetic acid (20 c.c.) was mixed with bromine (0·5 c.c., 1 mol.) and heated under reflux for 2 hr. On cooling, the mixture was diluted with water, neutralised with aqueous ammonia, and extracted with chloroform, and the chloroform extract was dried. After removal of most of the solvent, the concentrated solution (10 c.c.) was chromatographed on a column (30 × 2 cm.) of alumina (Spence type H), elution being followed by means of the hand spectroscope. The ætioporphyrin so obtained crystallised from chloroform–methanol as purple prisms (30 mg.), $\lambda_{max.}$ 399, 498, 534, 567, and 620 mμ (log ε 5·16, 4·09, 3·95; 4·78, and 3·63 respectively).

(iv) The previous experiment was repeated but with the addition of zinc acetate (500 mg.). The yield of ætioporphyrin, after isolation in a similar manner, was unchanged.

Ætioporphyrin I Palladium Complex.—(i) 5-Bromo-5′-bromomethyl-3,4′-diethyl-4,3′-dimethyldipyrromethene hydrobromide (above; 1·0 g.) and 3% palladium–strontium carbonate (6·0 g.) were heated in ethanol (400 c.c.) for 20 hr. After separation of the catalyst, the solvent was removed under reduced pressure. The residue was chromatographed in chloroform on alumina (Spence type H; 50 × 3 cm.), elution being followed by means of the hand spectroscope. The *product* crystallised from chloroform–methanol in purple needles (45 mg., 7·5%), m. p. 300—304° (Found: C, 65·8; H, 5·9; N, 9·85. $C_{32}H_{36}N_4Pd$ requires C, 65·9; H, 6·2; N, 9·6%), $\lambda_{max.}$ 231, 272, 335, 393, 512, and 547 mμ (log ε 4·39, 4·07, 4·18, 5·26, 4·11, and 4·58 respectively).

(ii) 5-Bromo-3,4′-diethyl-3′,4,5′-trimethyldipyrromethene hydrobromide perbromide (1·0 g.; above) and 3% palladium–strontium carbonate (6·0 g.) were heated in ethanol (400 c.c.) for 20 hr. The product (40 mg., 8%), isolated as in the foregoing experiment, was the same as the previous metal porphyrin.

We acknowledge the award of Maintenance Grants (to I. T. K., E. M., and K. B. S.) from the Department of Scientific and Industrial Research and we thank the directors of Imperial Chemical Industries Limited, Dyestuffs Division, for permission for one of us (R. P.) to take part in this work. Generous gifts of intermediates from the Distillers Company Ltd. are also gratefully acknowledged.

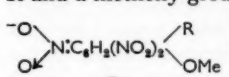
UNIVERSITY OF NOTTINGHAM. [*Received, April 16th*, 1959.]

690. *Coloured Alkali Salts from* sym.*-Trinitrobenzene Derivatives. Part I. Picryl Derivatives.*

By R. C. Farmer.

The reactions of the coloured compounds formed from trinitrobenzenes by the action of alcoholic alkalis have been studied. The products are quinonoid and contain two nitro-groups, a nitronate group and two *gem*-substituents, one of these being an alkoxy-group. This paper deals with products obtained from picryl compounds. In water these undergo two types of decomposition depending on pH. The free nitronic acids decompose very rapidly to the picryl compounds from which they were derived, but there are indications that this is slightly reversible. Picric acid forms the compounds with difficulty, but under certain conditions unstable red solutions can be obtained. The primary product of the action of a methoxide on picryl chloride, containing chlorine and a methoxy-group, acts in a dual capacity and leads to further reactions following two different routes, one of which is extremely rapid and the other very slow. Each of these leads to the same final product, methyl picrate.

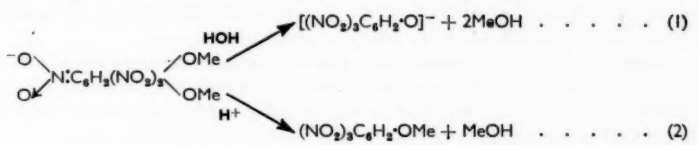
It has long been known that *sym.*-trinitrobenzene and its derivatives give strongly coloured solutions with alcoholic alkalis. The constitution based on Meisenheimer's [1] work is generally accepted.[2] According to this, a trinitrobenzene derivative, $(NO_2)_3C_6H_2R$, reacts with potassium methoxide, forming a quinonoid nitronate ion, (I), in which the substituent R and a methoxy-group are attached to the same carbon atom of the benzene ring. The anion has been assumed to be a resonance-hybrid of the *ortho*- and the *para*-quinonoid form.[3]



(I)

Picric esters form well-defined red crystalline salts with alcoholic alkalis. The salts are stable when dry. Jackson and Boos [4] found that alkoxy-groups are often interchangeable; *e.g.*, a methoxy-group can be gradually replaced by an ethoxy-group in ethanol solution. This was re-examined in the present work, as it might have affected the validity of Meisenheimer's work,[1] but the results showed that his deductions were not appreciably disturbed by an interchange of the groups.

In water, the coloured salts from picric esters undergo two types of decomposition:



Change (1) is gradual: (2) is very rapid and takes place *via* the nitronic acid. These acids are very weak and are set free by carbonic acid.

Picric acid does not normally form red compounds with methanolic alkali, but only picrate. Under certain conditions red solutions were obtained, indicating the formation of a hydroxy-methoxy-compound. Methyl picrate also reacted with aqueous alkali and should form the same product, but in each case the red solution soon gave the yellow picrate.

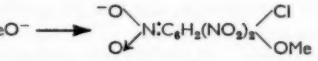
Picryl Chloride.—The interaction of equimolar proportions of picryl chloride and

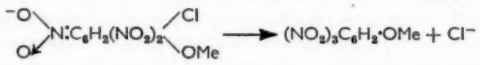
[1] Meisenheimer, *Annalen*, 1902, **323**, 205; 1907, **355**, 249. See also Jackson and Gazzolo, *Amer. Chem. J.*, 1900, **23**, 376; Jackson and Earle, *ibid.*, 1903, **29**, 89.
[2] Hantzsch and Picton, *Ber.*, 1909, **42**, 2119; Foster and Hammick, *J.*, 1954, 2153; Foster, *Nature*, 1955, **176**, 746; Bunnett, *Quarterly Reviews*, 1958, **12**, 1.
[3] Sidgwick, "The Organic Chemistry of Nitrogen," 1937, p. 260, Clarendon Press, Oxford.
[4] Jackson and Boos, *Amer. Chem. J.*, 1898, **20**, 444.

XUM

methanolic potash gives rise to a series of reactions. There are two stages; the first is very rapid and gives an intense colour. This is followed by a phase in which the red colour fades gradually. After some days the solution becomes pale yellow and yields methyl picrate. Part of the methyl picrate is formed in the first stage (about 40%) and the remainder in the second stage. Examination of the intermediate products leads to the following mechanism.

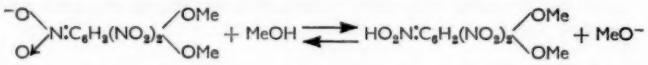
Stage I (very rapid at room temp.):

Reaction A. $(NO_2)_3C_6H_2Cl + MeO^- \longrightarrow$ 

Reaction Bi. 

Reaction Bii.

Stage II (gradual conversion of the product of Bii into methyl picrate):

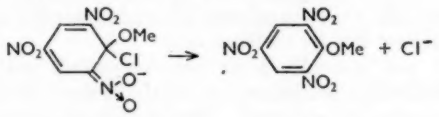
Reaction C. 

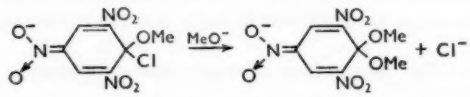
Reaction Di.

Reaction Dii. Action of MeO^- at very low concentration on residual picryl chloride.

Reaction A is the normal action of methoxide on a trinitrobenzene derivative. It gave a deep-red solution, and chloride ions were formed very rapidly. After a short time red crystals of $KO_2N{:}C_6H_2(NO_2)_2(OMe)_2,MeOH$ separated out. Unchanged picryl chloride was still present and the solution also contained methyl picrate. The formation of the above potassium salt in presence of picryl chloride was unexpected. The red salt might conceivably be formed by Reaction Bi, followed by conversion of the resulting methyl picrate into the dimethoxy-quinonoid nitronate, but in presence of picryl chloride this could occur only if methyl picrate were more reactive than picryl chloride towards methoxide. A separate experiment showed picryl chloride to be the more reactive. It follows that methyl picrate cannot be an intermediate in the formation of the red potassium salt in presence of picryl chloride. Reaction Bii was considered as an alternative, but this would not account for the presence of methyl picrate. Analysis of the products showed that both reactions proceeded simultaneously.

According to the accepted view the quinonoid nitronate ion can act either as an *ortho*- or a *para*-quinone. The probability is that the *ortho*-quinonoid compound gives methyl picrate by reason of the vicinity of the nitronate group to the chlorine, and the *para*-quinonoid compound reacts with a further methoxide ion.

Bi 

Bii 

In support of this it was found that addition of methyl picrate suppressed reaction Bi and gave a larger proportion of Bii. Reaction Bii must proceed more rapidly than reaction A, otherwise unchanged picryl chloride would not be present at the end of Stage I. The rates of reactions Bi and Bii appear to be of the same order.

It remained to explain the reason for the slow reaction. The transition from Stage I to Stage II is quite abrupt. As soon as the free methoxide is all consumed, the velocity falls to a very low level and the red colour begins to fade very slowly. This continues for 2—3 days; the colour has then become pale yellow and the solution contains only methyl picrate. The slowness of Stage II, in contrast to Stage I, points to an extremely low concentration of methoxide ions. A direct experiment on a mixture of picryl chloride and the nitronic compound gave a similar gradual fading of the red colour with formation of methyl picrate. This can be explained by the slight conversion of the nitronate ion as in reaction C, yielding the free nitronic acid and methoxide ions which react as in reactions Di and Dii, respectively. A synthetic mixture, consisting of picryl chloride, methyl picrate, and the nitronic sodium salt in the proportion resulting from reactions Bi and Bii, behaved in just the same way as the slow reaction in Stage II, and gave the same velocity of reaction.

Influence of Methyl Picrate.—Methyl picrate was found to have a retarding effect on the slow reaction. This is readily accounted for; reaction Di is to a slight extent reversible and is suppressed by methyl picrate. This increases the amount of free nitronic acid present, and this in its turn suppresses reaction C and so decreases the concentration of methoxide ions on which the velocity of Stage II depends.

Experimental

Nitronic Salts from Methyl Picrate and Methoxides.—The solvated *potassium* salt formed small, bright-red rhomboidal plates, mixed with small needles (Found: K, 11·3; loss at 75°, 9·4. $C_8H_5O_8N_3K,CH_3{\cdot}OH$ requires K, 11·3; $CH_3{\cdot}OH$, 9·3%). Dried *salt* (Found: K, 12·5. $C_8H_5H_8N_3K$ requires K, 12·5%); reabsorption of methanol (Found: increase of weight, 10·2. $CH_3{\cdot}OH$ requires 10·2%); absorption of acetone vapour (Found: increase of weight, 9·1. $\frac{1}{2}C_3H_6O$ requires 9·3%).

The solvated *sodium* salt formed large, bright red prisms with green shimmer (Found: loss on warming, 9·8. MeOH requires loss, 9·7%). Dried *salt* (Found: Na, 7·6. $C_8H_5O_8N_3Na$ requires Na, 7·7%). It absorbed moisture rapidly.

The solid salts are stable in absence of moisture and in methanolic solution. The potassium salt showed a loss of only 2% in a 0·15N-solution during 6 days at room temperature.

Action of Water, Acid, and Alkali.—An aqueous solution of the red potassium salt gradually turned yellow and after a few hours gave an almost quantitative yield of picrate. Weak aqueous alkali gave the same result. In presence of acid, the nitronic acid was liberated and decomposed at once to methyl picrate (yield 98—99%). Weak acids, including carbonic acid, precipitated methyl picrate, but phenol gave no precipitate. The red salt was slightly hydrolysed in aqueous solution. No solid separated out, but methyl picrate could be extracted by benzene.

Interchange of Alkoxy-radicals in Nitronic Salts.—On boiling with ethanol, the dimethoxy-quinonoid compound was partially converted into the diethoxy-compound. Red quinonoid compounds were prepared (*a*) from methyl picrate and ethoxide, (*b*) from ethyl picrate and methoxide. On acidification each of these gave a mixture of methyl and ethyl picrate. The m. p.s corresponded to 68·6 and 67·4% of ethyl picrate. The difference is small and does not affect Meisenheimer's conclusion.[1]

Picric Acid.—Picric acid as a rule yields only yellow picrate with methoxide, but on shaking a colourless solution of picric acid in toluene with sodium methoxide at 0°, a red solution was obtained. The converse reaction of methyl picrate with aqueous alkali also gave a red solution, but in each case the solution turned yellow in a short time.

Action of Methoxide on Picryl Chloride.—Methanolic potash (1 mol.) was mixed with picryl chloride (1 mol.) in methanol. An intense red colour was formed immediately. Silver nitrate showed rapid formation of chloride ions. This was followed shortly by a copious precipitation of bright red crystals, which were identified by crystal form and analysis as the above solvated potassium salt (Found: K, 11·2%). Acidification gave a 98·3% yield of methyl picrate, m. p. and mixed m. p. 67·5°. No trace of chlorine was found in the potassium, sodium, or barium salt. With excess of picryl chloride, the red potassium salt still separated out, but decreased in quantity. With 4 mols. of picryl chloride, 0·05 mol. of the solid potassium salt was obtained. Unchanged picryl chloride was still present, even in excess of methoxide up to nearly 2 mols.

Local interactions during mixing formed a serious source of error in estimating the reaction products, and it was essential to provide for instantaneous mixing of the reagents. A solution of picryl chloride in methanol was made up in a wide-mouthed bottle, and the methoxide solution was measured out in a thin-walled tube, which was lowered into the bottle. The whole was brought to the required temperature and at a given moment the bottle was shaken vigorously to break the inner tube. The Stage I reaction was completed immediately. Ice-cold water, free from carbon dioxide, was added to check further reaction and the mixture was tested.

The compounds present are the quinonoid nitronate, methyl picrate, and picryl chloride. The necessary data for the calculations are (1) the precise amounts of picryl chloride and methoxide taken, and (2) the quantity of the quinonoid nitronate formed. Tests on pure potassium quinonoid nitronate showed that it could be estimated accurately by titration with acid to the point at which the red colour just disappeared.

The method of deduction is best shown by an example. In the interaction of equimolar amounts of picryl chloride and methoxide at 20° the proportion of nitronate formed was 0·309 mol. Formation of the dimethoxy-quinonoid nitronate requires 2 equiv. of methoxide to one of picryl chloride. Hence 0·309 mol. of nitronate required 0·618 mol. of methoxide, leaving 0·382 mol. for the formation of methyl picrate, which requires 1 mol. of methoxide per mol. of picryl chloride. No other product can be present, for it is found that after long standing the sole product is practically pure methyl picrate (m. p. 67·5—68°), whereas if any compound other than methyl picrate or the nitronate were formed at an intermediate stage, it would be present in the final product and would depress the m. p. of the methyl picrate. No such depression was observed. Unchanged picryl chloride was also present. No satisfactory quantitative method of separation of picryl chloride and methyl picrate in a mixture could be found but, knowing with accuracy the quantity of picryl chloride used in the formation of the nitronate and the methyl picrate (*viz.*, 0·309 + 0·382 mol.), the remainder must be a close approximation to the unchanged picryl chloride. This amounts to 0·309 mol. It is seen to be equivalent to the amount of nitronate, and this fits in with the requirement that the two shall interact gradually, ultimately yielding methyl picrate as the sole product. A synthetic mixture of the products based on the above deduction gave the same velocity of reaction in stage 2 as was obtained with picryl chloride and the methoxide.

Relative Activity of Picryl Chloride and Methyl Picrate towards Methoxide.—1 Mol. of methoxide was added to a mixture of picryl chloride and methyl picrate (1 mol. of each) in methanol. If methyl picrate were the more reactive, the solution should contain 1 mol. of the nitronic compound and 1 mol. of unchanged picryl chloride. If picryl chloride were the more reactive, reaction Bi would be strongly suppressed by the large excess of methyl picrate and the solution should contain approx. 0·5 mol. of picryl chloride, 0·5 mol. of nitronic compound, and 1 mol. of unchanged methyl picrate. The nitronic compound found in two experiments was 0·52, 0·53 mol. Dilution with water, followed by extraction with benzene and evaporation, gave a residue which melted indefinitely up to 52°. These are in agreement with the latter alternative.

Effect of Ratio of Methoxide to Picryl Chloride.—Concn. of picryl chloride, 0·180N. Temp. 0°. The figures for methoxide added and resultant products are given in mols. per mol. of picryl chloride originally present.

Methoxide added	Nitronic compound formed	Methyl picrate formed (calc.)	Picryl chloride unchanged (calc.)
0·800	0·206	0·388	0·406
1·000	0·285	0·430	0·285
1·200	0·411	0·378	0·211
1·400	0·540	0·320	0·140
1·600	0·689	0·222	0·089
1·800	0·846	0·108	0·046
2·000	0·996, 0·997, 1·001	Nil	Nil

Influence of Variations in Temperature and Concentration of Picryl Chloride.—Mol. ratio of methoxide to picryl chloride = 1 : 1. Concn. 0·10N. Temp. 0°. Nitronic compound formed, 0·298. Temp. 20°. Nitronic compound formed, 0·333. Concn. 0·18N. Temp. 0°. Nitronic compound formed, 0·285. Temp. 20°. Nitronic compound formed, 0·309.

Effect of added Methyl Picrate.—Picryl chloride, 1 mol. Methoxide, 1 mol. Concn. 0·180N. Temp. 0°.

(i) Without addition of methyl picrate: Nitronic compound, 0·285 mol.

(ii) With addition of 0·5 mol. of methyl picrate: Nitronic compound, 0·433 mol.

Transition from Stage I to Stage II.—When the solutions of picryl chloride and methoxide were mixed by pipetting, local interactions led to an abnormally high formation of the nitronic compound, *e.g.*, 0·40—0·45. This gave rise to an indistinct transition phase, in which the velocity was intermediate between those of Stage I and Stage II. In the extreme limit of 0·5 mol. of nitronic compound, the rate of decrease at 0° was found to be as follows:

Time (min.)	0	5	10	20	30	70
Nitronic compound	0·500	0·472	0·465	0·415	0·381	0·297

On the other hand, when equimolar amounts of picryl chloride and methoxide were mixed instantaneously there was a sharply defined transition from the rapid phase to the slow phase, when the free methoxide was all consumed.

Initial Velocity of Stage II at 0°.

Time (min.)	1	5	20	360
Nitronic compound	0·286	0·283	0·279	0·251

Equimolar amounts of the red sodium nitronate and picryl chloride were dissolved in methanol (concn. 0·125N) and stored at room temperature. The colour gradually faded as in Stage II, and after 3 days most of the picryl chloride was converted into methyl picrate.

The following Table shows the course of Stage II. The initial concentration of picryl chloride and methoxide was 0·180N. The data show mols. of products per mol. of picryl chloride.

Velocity of slow reaction (*Stage II*).

(i) Temp. 0°.							
Time (hr.)	0·03	6	24	48	72	96	120
Nitronic compound	0·285	0·251	0·181	0·132	0·096	0·081	0·065
Methyl picrate (calc.)	0·430	0·498	0·638	0·736	0·808	0·838	0·870
Picryl chloride (calc.)	0·285	0·251	0·181	0·132	0·096	0·081	0·065

(ii) Temp. 20°.								
Time (hr.)	0·05	0·25	1	2	3	4	5	6
Nitronic compound	0·309	0·284	0·231	0·185	0·157	0·137	0·120	0·108
Methyl picrate (calc.)	0·382	0·432	0·538	0·630	0·686	0·726	0·760	0·784
Picryl chloride (calc.)	0·309	0·284	0·231	0·185	0·157	0·137	0·120	0·108

For comparison, a synthetic mixture was made up corresponding to the product of Stage I at 20°, and the velocity measured. The nitronic compound decreased from 0·310 to 0·106 mol. in 6 hr. at 20°. This agrees closely with the above Table, which showed a decrease from 0·309 to 0·108 mol. in 6 hr.

Retardation of Stage II by Methyl Picrate.—The product of Stage I normally contained 0·430 mol. of methyl picrate at 0°, and the nitronic compound decreased from 0·285 to 0·181 mol. in 24 hr. at 0°. A synthetic mixture of the same composition, but without the methyl picrate, showed a decrease of the nitronic compound from 0·286 to 0·096 mol. in 24 hr.

In another experiment excess of methyl picrate was added. In the normal reaction at 20° the methyl picrate present immediately after the transition from Stage I to Stage II was 0·382. This was increased to 0·882 mol. by addition of methyl picrate. The nitronic compound decreased from 0·309 to 0·167 after 4 hr. at 20°, as against 0·137 when no additional methyl picrate was present. Thus in each case methyl picrate showed a retarding action.

Reversibility of Decomposition of the Quinonoid Nitronic Acid.—On acidification of the nitronic salt in aqueous solution, the nitronic acid liberated decomposed at once to methyl picrate and methanol. In methanolic solution the decomposition was appreciably retarded, as shown by the rate of fading. This was more marked in presence of methyl picrate. A methanolic solution of the free nitronic acid (concn. 0·035N) faded in approx. 5 min. In presence of 5 mols. of methyl picrate per mol. of nitronic acid the colour persisted for over an hour. It passed through a yellow stage [5] before becoming colourless. In aqueous solution the nitronic salt was slightly hydrolysed, but no methyl picrate separated out. On addition of 10 c.c. of benzene to a solution of 1 g. of the nitronic salt in 100 c.c. of water at 20° and shaking, 0·122 g. of methyl picrate was extracted. If the conversion of the nitronic acid into methyl picrate was irreversible, further

[5] Cf. Aynscough and Caldin, *J.*, 1956, 2528; Foster, *Nature*, 1959, **183**, 1043.

hydrolysis should take place until the whole of the free nitronic acid was converted into methyl picrate. On addition of methanol to a colourless solution of methyl picrate in benzene, it gradually turned orange-yellow. A comparative experiment with dinitrotoluene gave no colour.

The author thanks Professor D. H. Hey, F.R.S., for the facilities provided for the work described in this and following parts, and for his interest and advice.

KING'S COLLEGE, STRAND, LONDON, W.C.2. [*Received, April 24th*, 1959.]

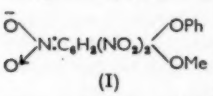
---

691. *Coloured Alkali Salts from* sym.*-Trinitrobenzene Derivatives. Part II.* Phenoxy-compounds.*

By R. C. FARMER.

The action of alcohols on trinitrobenzene derivatives in presence of alkali was dealt with in Part I. Further experiments showed that this reaction was not confined to alcohols: other hydroxy-compounds (phenols, carboxylic acids, oximes) gave similar reactions. The phenoxy-compounds are dealt with in the present Part. They are analogous to the alkoxy-derivatives, but are very unstable, being readily dissociated to the free nitronic acids, which decompose immediately to the trinitro-compounds from which they were derived. The phenoxy-groups are also very readily displaced by methoxy-groups in presence of methoxide. It has not been found possible to reverse this displacement.

THE formation of intense red colours on addition of alcohols to trinitrobenzene derivatives in presence of alkali suggested the possibility of using this reaction for the detection of small quantities of alcohols. Qualitative tests showed, however, that other hydroxy-compounds gave similar reactions. Numerous phenols and carboxylic acids gave positive results. The hydroxy-group appears to be necessary; thus phenol reacts, but anisole does not. Alkali is also necessary to the reaction. Acids destroy the colour at once and regenerate the corresponding trinitro-compounds. Thus, the dimethoxy-quinonoid nitronate yields methoxy-trinitrobenzene; the diphenoxy-compound yields phenoxy-trinitrobenzene (2,4,6-trinitrodiphenyl ether). The phenoxy-quinonoid nitronates are very strongly hydrolysed in aqueous solution and are stable only in presence of a considerable excess of alkali. By analogy with the alkoxy-trinitrobenzene compounds, phenoxytrinitrobenzene would be expected to give the ion of a mixed methoxy-phenoxy-compound (I) with methoxide. The phenoxy-group was, however, at once split off and replaced by a methoxy-group. It is probable that the mixed methoxy-phenoxy-compound was formed momentarily; an analogous instance is given in the following paper, in which a methylnitramino-group is split off by methoxide, but in this case the reaction was relatively slow and it was possible to show that the compound initially formed contained a methoxy-group and a methylnitramino-group.



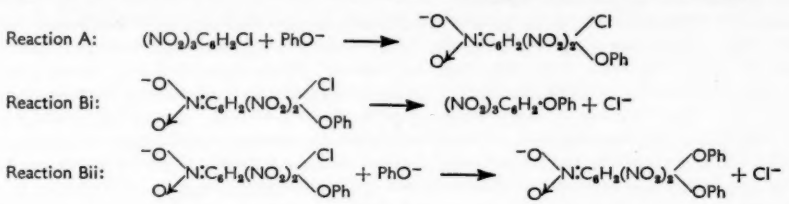
(I)

A solution of potassium phenoxide in methanol contains a small proportion of methoxide, and on account of the much greater reactivity of methoxide there is a marked tendency for the action of such a solution on picryl chloride to yield the methoxy- instead of the phenoxy-compound. This can be suppressed by the addition of phenol, and under these conditions trinitrodiphenyl ether can be obtained pure and in good yield.

The action of potassium phenoxide on picryl chloride in methanol is analogous to that of methoxide, forming a phenoxy-quinonoid compound which leads to trinitrodiphenyl

* Part I, preceding paper.

ether; but whereas in the latter case there are two distinct stages, the first almost instantaneous and the second very slow, the action of phenoxide is very rapid throughout. The stages in the formation of trinitrodiphenyl ether appear to be the following:



The diphenoxy-compound then dissociates to the free nitronic acid which decomposes to trinitrodiphenyl ether.

Reaction A is the normal reaction of a trinitrobenzene derivative (Part I). The formation of an unstable quinonoid compound is indicated by the evanescent red colour. The presence of the phenoxy-group is shown by the subsequent conversion into trinitrodiphenyl ether. It is supported by experiments in aqueous alkali in which the quinonoid nitronates are more stable.

Reaction B—in the action of methoxide on picryl chloride (Part I) it was found that about 40% of the picryl chloride acted as in reaction Bi and about 30% as in Bii, the rest being unchanged picryl chloride which entered into the reaction at a subsequent stage. In the action of phenoxide, the whole series of reactions occurred so rapidly that the proportions could not be determined. Reaction Bi leads directly to trinitrodiphenyl ether, whereas Bii is less direct and involves the presence of free picryl chloride in the later stage. Experiment showed that the formation of trinitrodiphenyl ether took place more readily when picryl chloride was present, but could nevertheless take place in absence of free picryl chloride. This appears to indicate that the two reactions occur simultaneously. The diphenoxy-quinonoid nitronate very readily yields the free nitronic acid, as shown by its hydrolysis in aqueous solution, and the free acid decomposes at once to trinitrodiphenyl ether. This immediate dissociation contrasts with the slow dissociation of the dimethoxy-compound (Part I), and accounts for the rapidity of the latter phase of the reaction.

Experimental

Test for Interaction of Hydroxy-compounds with Trinitrobenzene Derivatives.—A small quantity of the test substance was added to a saturated solution of trinitrotoluene in benzene and a drop of a saturated aqueous sodium hydroxide was added and well mixed. This formed a brownish sludge of the di- or tri-nitronate. Benzene was added to dilute the trinitrotoluene, and excess of water was added. The di- or tri-nitronate was converted into the quinonoid mononitronate, which gave a red solution. These conditions were necessary to inhibit the direct action of aqueous alkali on trinitrotoluene. Alcohols gave a strong reaction. Other hydroxy-compounds gave similar results, in particular numerous phenols and carboxylic acids. Mononitrophenols (*o*, *m*, *p*) reacted strongly, 2,4-dinitrophenol somewhat less strongly, and even trinitrophenol, functioning as a hydroxy-compound, gave a distinct reaction.

Action of Aqueous Phenoxide on Picryl Chloride.—A solution of picryl chloride in benzene (20%) was stirred vigorously with potassium phenoxide and alkali in aqueous solution. In dilute alkali no red colour was formed, but with 1·5—3·5N-alkali the solution became strongly red. On acidification the red colour disappeared at once and trinitrodiphenyl ether separated (m. p. and mixed m. p. 152—153°). Yields of 85—86% were obtained. The alkaline solutions were still red after 2 weeks at 0°, but trinitrodiphenyl ether separated out gradually. In alkali of lower concentration the red compounds were hydrolysed rapidly, with separation of trinitrodiphenyl ether. In concentrated alkali (16N) only an orange colour appeared (dinitronate), but on dilution to 2N the strongly coloured mononitronate was formed. On further dilution trinitrodiphenyl ether separated. The majority of organic solvents were unsuitable as solvents.

Liquid phenols were too acid and most other solvents gave unsatisfactory results, as it was

XUM

impossible to add sufficient alkali. Small yields of solids were obtained in some cases, but these did not give trinitrodiphenyl ether on acidification. Jackson and Earle,[1] using a mixture of ether and phenol, obtained a solid product, but no reactions were given and the presence of phenol appears to rule out this method.

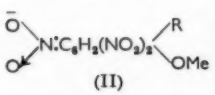
Action of Phenoxide on Picryl Chloride in Methanol.—On addition of a methanolic solution of potassium phenoxide to picryl chloride, it frequently happened that the dimethoxy-compound was formed instead of the phenoxy-derivative. An increase in the proportion of phenoxide up to 10 mol. gave no better result. It was necessary to suppress the methoxide ions to a minimum. The best results were obtained with about 1·05 mol. of phenoxide and 0·2 mol. of phenol per mol. of picryl chloride. The phenoxide solution was added slowly, as recommended by Willgerodt,[2] a transient red colour being formed with each drop. Chloride ions were formed rapidly and trinitrodiphenyl ether separated out (yield 86—88%; m. p. and mixed m. p. 153°). No dimethoxy-compound was present under these conditions, as shown by the rapid disappearance of the red colour (a methanolic solution of the red dimethoxy-compound retains its colour for weeks unchanged). Although the trinitrodiphenyl ether contained no dimethoxy-compound, it was frequently found that when the product was left in contact with the mother-liquor for a few hours, small red crystals of the potassium dimethoxy-compound were formed (about 1%) (Found: K, 11·2. Calc. for $C_8H_8O_8N_3K,CH_3{\cdot}OH$: K, 11·3%). A similar formation of these red crystals occurred when potassium phenoxide was added to trinitrodiphenyl ether in methanol.

Influence of Free Picryl Chloride in Solution during Reaction.—(1) Picryl chloride present in solution throughout the reaction; yield of trinitrodiphenyl ether, 84%. (2) Practically no free picryl chloride in solution during the mixing; yield, 61%. (3) Reagents mixed instantaneously; yield, 75%.

Action of Methanolic Potash on 2,4,6-Trinitrodiphenyl Ether and Derivatives.—On addition of methanolic potash to trinitrodiphenyl ether a deep red solution was obtained, but none of the expected methoxy-phenoxy-quinonoid nitronate was found. The phenoxy-group was at once split off and replaced by a methoxy-group, forming the dimethoxy-compound, which separated in the characteristic red crystals of its methanol solvate (yield, 91%) (Found: K, 11·15%). Acidification gave 96% of methyl picrate, m. p. 67°. The phenol resulting from the splitting off of the phenoxy-group was found in the filtrate from the red crystals.

Ethanolic potash reacted similarly, giving crystals of the diethoxyquinonoid nitronate (Found: K, 11·6. $C_{10}H_{12}O_8N_3K$ requires K, 11·5%). Acidification gave 96% of ethyl picrate, m. p. 78°, and the filtrate from the red crystals contained phenol.

The splitting off of the phenoxy-group takes place only in presence of alkali; boiling methanol or ethanol had no action on trinitrodiphenyl ether. The following trinitrodiphenyl ether derivatives were examined. In each case the primary product (II) was converted at once into (II; R = OMe), which separated as the potassium salt and was identified by crystal form, analysis, and conversion into trinitroanisole (m. p. 67·5°). The filtrate gave on acidification the substituted phenol corresponding to the group R.



(II)

3-Methyl-2′,4′,6′-trinitrodiphenyl ether was prepared from picryl chloride and potassium *m*-tolyloxide in methanol (yield, 84%), m. p. 149·5° (Found: C, 49·0; H, 2·8; N, 13·4. $C_{13}H_9O_7N_3$ requires C, 48·9; H, 2·8; N, 13·2%). It reacted as above; the nitronic potassium salt separated out and the filtrate contained *m*-cresol.

2,4,6,2′-Tetranitrodiphenyl ether. The nitrophenoxy-group was replaced by a methoxy-group. The solid product was the potassium dimethoxyquinonoid nitronate; the filtrate contained *o*-nitrophenol, m. p. 44°.

2,4,6,3′-Tetranitrodiphenyl ether. The solid product was as above and the filtrate contained *m*-nitrophenol, m. p. 96°.

2,4,6,4′-Tetranitrodiphenyl ether. The solid product was again the above potassium salt, and the filtrate contained *p*-nitrophenol, m. p. 114°.

2,4,6-Tribromo-2′,4′,6′-trinitrodiphenyl ether was prepared from picryl chloride and potassium tribromophenoxide in ethanol; it formed pale yellow, thick hexagonal laminæ, m. p. 179° (Found: C, 26·6; H, 1·0; N, 7·94. $C_{12}H_4O_7N_3Br_3$ requires C, 26·6; H, 0·7; N, 7·75%), and yielded the nitronic potassium salt and tribromophenol, m. p. 95°.

[1] Jackson and Earle, *Amer. Chem. J.*, 1903, **29**, 89.
[2] Willgerodt, *Ber.*, 1879, **12**, 1278.

Phenylazophenyl picrate was prepared from potassium phenylazophenoxide and picryl chloride in acetone–alcohol; it had m. p. 186° (Found: C, 52·7; H, 2·4; N, 17·3. $C_{18}H_{11}O_7N_5$ requires C, 52·8; H, 2·7; N, 17·1%), and yielded the nitronic potassium salt and phenylazophenol, m. p. 153°.

2,4,6,2′,4′,6′-Hexanitrodiphenyl Sulphide.—This contains two trinitrophenyl groups, but only one of these formed a nitronic compound. As in the above compounds, methanolic potash gave the dimethoxy-quinonoid nitronate (0·98 mol.) and the remainder of the molecule, $\cdot S\cdot C_6H_2(NO_2)_3$, was split off. It showed considerable decomposition. Thiopicric acid could not be identified.

All attempts to replace methoxy- or ethoxy-groups by phenoxy-groups in the quinonoid nitronates gave negative results.

King's College, Strand, London, W.C.2. [*Received, April 24th*, 1959.]

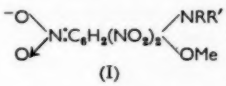
---

692. *Coloured Alkali Salts from* sym.-*Trinitrobenzene Derivatives. Part III.* Picramide Derivatives.*

By R. C. Farmer.

The coloured quinonoid nitronates obtained by the action of methoxide on picramide derivatives have been examined. Two alternative methods of preparation are given, proceeding by different routes. The coloured amino-compounds differ from the corresponding phenoxy-compounds, in that they lose their methoxy-groups on acidification and the amino- or anilino-group remains attached to the benzene ring. Trinitrophenylmethylnitramine was included as a nitramine. The splitting off of the methylnitramino-group was gradual and its separation was followed by sampling at intervals. A secondary reaction was found to occur, in which a nitro-group in the benzene ring was replaced by a methoxy-group, forming two isomeric compounds, 2-methoxy-4,6- and 4-methoxy-2,6-dinitrophenylmethylnitramine.

Picramide and its *N*-methyl and *N*-phenyl derivatives react with methoxide in the same manner as trinitrobenzene, forming coloured solutions; some solid salts have been obtained by Busch and Kögel.[1] It is now found that the coloured compounds can be obtained by two methods. Thus, the salt of an ion (I; R′ = H) can be made (1) by the action of methoxide on the aniline $(NO_2)_3C_6H_2\cdot NHR$, and (2) by the action of the amine $R\cdot NH_2$ on the anisole $(NO_2)_3C_6H_2\cdot OMe$.



(I)

The amino- or anilino-group is more firmly bound than the phenoxy-group, and whereas in the methoxy-phenoxy-quinonoid nitronates (Part II) the phenoxy-group was very readily split off and replaced by a methoxy-group, yielding trinitroanisole on acidification, the amino- or anilino-methoxy-compounds lose the methoxy-group on acidification and the amino- or anilino-group remains intact. It was not found possible to make coloured quinonoid nitronates containing two anilino-groups attached to the same carbon atom.

Trinitrophenylmethylnitramine (tetryl) was included as an example of a nitroamine. It reacted with methoxide forming a salt of the ion (I; R = NO_2, R′ = Me). This remained intact sufficiently long to enable it to be identified, but gradually lost the methylnitramino-group.

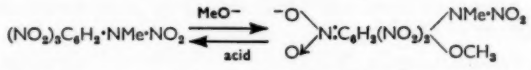
Tetryl reacted also with aqueous alkali, giving an intense red colour. On acidification immediately after mixing, pure tetryl was recovered, showing that the methylamino-group remained intact for a time, but decomposition slowly set in with formation of picric acid, etc.

* Part II, preceding paper.

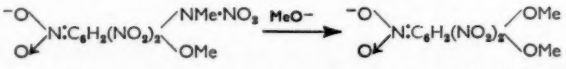
[1] Busch and Kögel, *Ber.*, 1910, **43**, 1549.

By-products of the Action of Methanolic Potash on Trinitrophenylmethylnitramine.—The yields of the methoxy-quinonoid compound fell considerably short of theory (60—65%). About 20% of a mixture of by-products was obtained. Two isomeric compounds were isolated and were identified as 2-methoxy-4,6- and 4-methoxy-2,6-dinitrophenylmethylnitroamine. This indicates that a nitro-group in the benzene nucleus was replaced by a methoxy-group. The action of methoxide on trinitrophenylmethylnitramine is thus as follows:

(1) Primary reaction. Formation of nitronic compound:

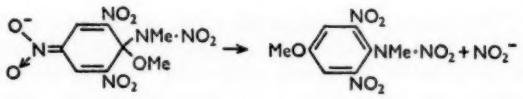


followed by gradual replacement of the methylnitramino-group by methoxy:

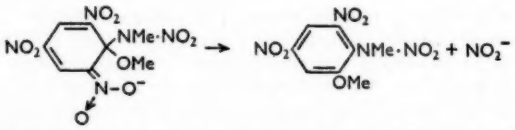


(2) Secondary reaction. Conversion of nitrone into methoxydinitrophenylmethylnitramines:

(a)



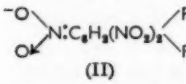
(b)



These have been previously synthesized by other methods, and their properties and reactions agree with the products obtained from tetryl in the present work. Their formation supports the generally accepted assumption that the coloured anions formed from trinitrobenzene derivatives are resonance hybrids intermediate between the two quinonoid forms.[2] The analogous replacement of a nitro-group by a methoxy-group was observed by Lobry de Bruyn [3] in the conversion of trinitrobenzene into dinitroanisole by sodium methoxide. This was confirmed in the present work. In this case two isomers are not possible, owing to the symmetry of the trinitrobenzene. In the case of trinitroanisole two isomers might be formed, but it was not found possible to obtain a product in which a nitro-group was substituted by a methoxy-group.

Experimental

Quinonoid Nitronates from Picramide Derivatives.—The following derivatives of the anion (II) have been examined. (i) R = NH_2, R′ = OMe. Picramide reacted with methanolic potash giving a deep red colour, and crystals of the quinonoid nitronate separated. The same product was obtained conversely from trinitroanisole and ammonia in methanol, followed by the addition of sufficient alkali to form the potassium salt (Found: K, 12·95. Calc. for $C_7H_7O_7N_4K$: K, 13·1%). Acidification regenerated picramide, m. p. 189°. No trinitroanisole was found.



(II)

(ii) R = NH_2, R′ = OEt. Analogous reactions of picramide with ethanolic potash, and of trinitrophenetole with ammonia plus alkali, gave red crystals which, on acidification, yielded picramide, m. p. 189°. No trinitrophenetole was formed.

[2] Sidgwick, "The Organic Chemistry of Nitrogen," 1937, p. 260, Clarendon Press, Oxford.
[3] Lobry de Bruyn, *Rec. Trav. chim.*, 1890, **9**, 208.

(iii) R = NHMe, R′ = OMe. *N*-Methylpicramide gave a deep red colour with methanolic potash, but no solid separated. On acidification the methoxy-group split off and *N*-methylpicramide, m. p. 111°, was regenerated.

(iv) R = NHPh, R′ = OMe. 2,4,6-Trinitrodiphenylamine gave a deep red solution with methanolic potash, and 2,4,6-trinitroanisole reacted similarly with aniline and alkali. In each case, trinitrodiphenylamine was recovered on acidification, m. p. 176—177°.

(v) R = NHPh, R′ = OEt. Ethanolic potash reacted with 2,4,6-trinitrodiphenylamine, and conversely aniline reacted with trinitrophenetole, giving very dark crystals. In each case acidification gave trinitrodiphenylamine, m. p. and mixed m. p. 177°. No trinitrophenetole was detected.

(vi) R = *p*-NH·C_6H_4Me, R′ = OMe. *N*-2,4,6-Trinitrophenyl-*p*-toluidine reacted with methoxide, and conversely 2,4,6-trinitroanisole reacted with *p*-toluidine, giving dark crystals. Each of the products gave *N*-trinitrophenyl-*p*-toluidine on acidification, m. p. 162°. In general, these nitronates are unstable to moisture.

(vii) R = R′ = NHPh. An attempt to prepare this compound by the action of aniline on trinitrodiphenylamine in presence of alkali was unsuccessful: no coloured compound was formed.

Trinitrophenylmethylnitramine (Tetryl).—Methanolic potash gave a deep red, clear solution. To ensure that no unchanged tetryl was present in the clear solution, the methanol was diluted to 50% with water, thus reducing the solubility of tetryl to about 1 in 4000. In the compound formed (I; R = NO_2, R′ = Me), the methylnitramino-group was more firmly attached than the methoxy-group. Addition of acid shortly after mixing regenerated tetryl almost quantitatively, m. p. and mixed m. p. 128°. Samples were taken at intervals and acidified; m. p.s of the products were as follows:

Time (min.) at 0—5°	1	3	7	19	44
M. p. to complete fusion	128°	126°	123°	115°	107°

The potassium salt, $KO_2N{:}C_6H_2(NO_2)_2(OMe)_2$ gradually separated. After long standing the acidified product from the solution was 2,4,6-trinitroanisole, m. p. 68°. Similar results were obtained with ether oxide. Acidification shortly after mixing gave pure tetryl (m. p. 128°); on long standing trinitrophenetole was obtained (m. p. 78·5°). Aqueous alkali reacted rapidly with tetryl, giving a clear, deep red solution. On acidification immediately after mixing, pure tetryl was regenerated. After some hours the methylnitramine group was decomposed by the alkali, forming acidic products (picric acid, etc.). When the alkali present was insufficient to neutralize the acids, some re-precipitation of the tetryl took place.

Aqueous ammonia reacted with tetryl, giving a deep red solution. Some picramide was formed (m. p. 190°).

By-products from Tetryl.—The yields of the dimethoxy-quinonoid nitronate depended on the alkali ratio and to a minor extent on the temperature and time of action. With 0·15 mol. of tetryl per l. at room temperature the yields were as follows:

Alkali ratio	0·67	1·00	1·18	2·00	2·51	5·0
Yield (%)	16	34	44	63	62	62

To account for the relatively low yields, the red sodium nitronate was converted into soluble picrate by dissolving it in water and allowing it to stand. A mixture of by-products remained insoluble. Under favourable conditions these amounted to 20%. They were practically colourless, showing absence of a quinonoid structure, and melted indefinitely at 85—120°. Nitrite was formed, indicating the loss of a nitro-group. The methylnitramino-group was still intact, as shown by the formation of nitric acid on addition of concentrated sulphuric acid,[9] and by the evolution of nitrous fumes on heating the dry compounds. Hence, a nitro-group in the benzene ring must have been split off. The compound was a dinitrobenzene derivative, as shown by the action of alkali in pyridine (purple colour) and by Janowski's test. Alcoholic alkali gave no colour in the cold (absence of trinitro-compound); a bright red colour was formed on warming, but disappeared on cooling. The compounds were insoluble in aqueous alkali (absence of phenols). Ferric chloride gave no colour.

The recorded observation of the conversion of trinitrobenzene into dinitroanisole by alcoholic alkali [3] was confirmed (yields 78—80%). By analogy with this, tetryl should give methoxydinitrophenylmethylnitroamine.

XUM

On separation, the by-products yielded two compounds, m. p. 117—118° and 124—125° respectively. Analysis showed them to be isomers of the composition $C_8H_8O_7N_4$ (Found, for former compound: C, 35·55; H, 3·1; N, 20·5; for latter compound: C, 35·5; H, 3·0; N, 20·4. Calc. for $C_8H_8O_7N_4$: C, 35·3; H, 3·0; N, 20·6%). The compound of m. p. 125° usually crystallised in prisms, but some thick hexagonal plates of the same m. p. were obtained. The compound of m. p. 118° crystallised in thin laminæ. That of m. p. 125° was identified as 4-methoxy-2,6-dinitrophenylmethylnitramine, which had been made by Réverdin;[4] it agreed with the published work in (1) m. p. 125°, (2) formation of a bright red colour, turning pale orange, on addition of concentrated sulphuric acid, (3) Liebermann's reaction (intense blue), (4) conversion into 4-methoxy-*N*-methyl-2,6-dinitroaniline (m. p. 129°) on boiling with a pentyl alcohol solution of phenol containing a little sulphuric acid, as described by Pinnow.[5] This compound was reconverted into the methylnitramine, m. p. 125°, by nitric acid.

The compound of m. p. 118° had been synthesized by several methods and established as 2-methoxy-4,6-dinitrophenylmethylnitramine. As stated by Réverdin,[6] it gave the Liebermann reaction, and with concentrated sulphuric acid gave a green solution fading slowly to dull brown. On heating with phenol and sulphuric acid in pentyl alcohol it gave 2-methoxy-*N*-methyl-4,6-dinitroaniline, m. p. 168°, in agreement with v. Romburgh.[7]

Tetryl, on similar treatment, gave *N*-methyltrinitrophenylaniline,[8] m. p. 111°, and this was reconverted into tetryl (m. p. and mixed m. p. 129·5°) by nitric acid.

King's College, Strand, London, W.C.2. [*Received, April 24th,* 1959.]

[4] Réverdin, *J. prakt. Chem.*, 1911, **83**, 165; 1911, **84**, 555.
[5] Pinnow, *Ber.*, 1897, **30**, 838.
[6] Réverdin, *J. prakt. Chem.*, 1910, **81**, 182.
[7] v. Romburgh, *Compt. rend.*, 1891, **113**, 506.
[8] v. Romburgh, *Rec. Trav. chim.*, 1886, **5**, 240.
[9] Thiele and Lachmann, *Annalen*, 1895, **288**, 269.

---

693. *Physicochemical Studies on Starches. Part XX.* The Existence of an Anomalous Amylopectin in Starch.*

By W. Banks and C. T. Greenwood.

The polysaccharide from the supernatant liquor from the recrystallisation of the initial amylose-complex of potato starch has a significantly lower average chain length and β-amylolysis limit than amylopectin. A similar polysaccharide occurs in rubber-seed starch. This material, which represents 5—10% of the granule, is thought to be inherent in the granular structure. Its physical properties are discussed.

Although the dual-component nature of the starch granule is well established,[1] there are reports of the existence of material with properties different from those of amylose and amylopectin. From a comprehensive study of the iodine affinities of various fractions and subfractions of amylose, Schoch and his co-workers [2] have suggested that in maize starch there may be 5—7% of such a substance. This polysaccharide was apparently precipitated by "Pentasol" but not by butan-1-ol. On the basis of optical-density and β-amylolysis measurements on mixtures of pure potato amylose and amylopectin, Peat, Pirt, and Whelan [3] postulated that potato starch granules may contain material with a higher iodine affinity but a lower β-amylolysis limit than amylopectin. An anomalous "thymol-amylopectin" has been isolated from the supernatant liquors from the recrystallisation of the initial thymol-amylose complex of potato starch by Cowie and

* Part XIX, *Stärke*, in the press.

[1] See Greenwood, *Adv. Carbohydrate Chem.*, 1956, **11**, 335.
[2] Lansky, Kooi, and Schoch, *J. Amer. Chem. Soc.*, 1949, **71**, 4066.
[3] Peat, Pirt, and Whelan, *J.*, 1952, 705.

Greenwood.[4] Recently, Perlin [5] has isolated a similar fraction (termed "Amylopectin-C") from wheat starch, whilst a second component, of low molecular weight, in waxy maize starch has been reported from sedimentation studies by Erlander and French.[6] In this paper, we give the results of detailed investigations made on the "thymol-amylopectin" isolated from potato starch and rubber-seed starch.

Experimental

Methods of isolating potato starch (vars.: Epicure = potato 1; Redskin = potato 2; Golden wonder = potato 3) and fractionating it so as to obtain the "thymol-amylopectin" have been described previously.[4] The polysaccharide was isolated by freeze-drying the supernatant liquor which had been concentrated to small volume under reduced pressure (temp. $<35°$). For Epicure starch, fraction 1A was isolated in this way, whilst fraction 1B was obtained by freeze-drying the supernatant directly. All samples were exhaustively extracted with boiling methanol. The sample of polysaccharide from rubber-seed starch had been isolated in earlier work.[7] Samples were characterised by measurements of iodine affinity (I.A.), average length of unit-chain ($\overline{C.L.}$), limiting viscosity number $[\eta]$, and percentage conversion to maltose on β-amylolysis (see earlier papers in this series [7]). The percentage of phosphorus in some samples was determined by wet oxidation of the polysaccharide with perchloric acid,[8] followed by colorimetric estimation of the phosphomolybdate complex as described by Fogg and Wilkinson.[9] (Sample weights of *ca.* 250 mg. were taken, and results were reproducible to $\pm 5\%$.)

Subfractionation of "thymol-amylopectin." A 0·25% aqueous solution of the Epicure potato "thymol-amylopectin" (250 ml. containing 0·1% of sodium chloride) was kept at 30°. Ethanol was added slowly with vigorous mechanical stirring until a permanent turbidity was observed (some 20% by volume was required). The temperature was then raised until the turbidity disappeared (50—55°), and the flask was then allowed to cool to 30° during 6 hr. After a further 48 hr. at this temperature, the supernatant liquor was decanted from the precipitated gel. A second fraction was precipitated by raising the alcohol concentration to 40%. Both fractions were dispersed in water and freeze-dried to yield fractions 1C and 1D, respectively. (Each fraction contained *ca.* 50% of the original polysaccharide.)

Results and Discussion

The results shown in the Table indicate that about 5—10% of potato starch appears to be precipitated with the initial thymol-amylose complex, and can be isolated from the recrystallisation liquors. A similar result has been found with butan-1-ol as the initial precipitant, but other reagents have not been investigated. This polysaccharide has a low iodine affinity, but a significantly lower chain length and β-amylolysis limit than amylopectin. The material would normally be discarded during fractionation.

The values of chain length and β-amylolysis limit for the "thymol-amylopectin" from rubber-seed starch and the "Amylopectin-C" from wheat starch are comparable to those for the potato polysaccharide. It is therefore suggested that such a polysaccharide might be a universal constituent of starches.

Adsorption of this branched polysaccharide on the initial amylose complex is unlikely, for the iodine affinity of the complex was unaltered by repeated washing with thymol-saturated water, or varying the force-field used in the isolation, or using butan-1-ol instead of thymol. Further, on dispersion of a starch, which had been previously leached with water at 65° and had lost about 60% of its amylose, the resultant amylose–thymol complex was 45% pure. If it is assumed that the same amount of branched polysaccharide is co-precipitated, the calculated purity of the complex is *ca.* 50%. This agrees well with the

[4] Cowie and Greenwood, *J.*, 1957, 4640.
[5] Perlin, *Canad. J. Chem.*, 1958, **36**, 810.
[6] Erlander and French, *J. Amer. Chem. Soc.*, 1958, **80**, 4413.
[7] Greenwood and Robertson, *J.*, 1954, 3769; Cowie and Greenwood, *J.*, 1957, 2658; Bryce, Cowie, Greenwood, and Jones, *J.*, 1958, 3558.
[8] Smith, *Analyt. Chim. Acta*, 1953, **8**, 397.
[9] Fogg and Wilkinson, *Analyst*, 1958, **83**, 406.

XUM

observed value. It is not known why co-precipitation should occur. There was the possibility that the phosphate groups in potato starch were predominantly associated with this fraction, but the "thymol-amylopectin" from Epicure starch contained 0·07% of phosphorus, whilst there was a similar amount (0·09%) in the corresponding amylopectin.

Properties of amylopectin-type polysaccharides in starches.

Starch	Component		Amount (%) [a]	Amylose (%) [b]	$\overline{C.L.}$	β-Limit [c]	External chain length [d]	[η]
Potato	Amylopectin 1		~75	0·5	23·1	57	15·7	190
	"Thymol-amylopectin"	1A	5—10	1·0	13·4	53	9·6	170
	" "	1B	5—10	0·5	13·6	51	9·4	150
	" "	1C	—	—	13·8	52	9·7	—
	" "	1D	—	—	14·0	50	9·5	—
	Amylopectin 2		~75	0·5	23·3	57	15·9	200
	"Thymol-amylopectin"	2	5—10	5·0	14·7	53	9·3	220
	Amylopectin 3		~75	1·0	23·2 *	56	15·5	180
	"Thymol-amylopectin"	3	5—10	2·0	15·8 *	—	—	76
Rubber-seed	Amylopectin		~70	0·5	23·1 *	64	17·3	—
	"Thymol-amylopectin"		10	2	15·8 *	61	12·1	—
Wheat †	Amylopectin		~70	low	Not accurately measured	55—60	—	—
	"Amylopectin C"		5—10	low		48—53	—	—

[a] % of total starch. [b] Calc. from iodine affinity. [c] Expressed as percentage conversion into maltose. [d] Calc. from $\{[\overline{C.L.} \times (\beta\text{-limit})] + 2{\cdot}5\}$.

* Results by courtesy of Mr. J. Thomson. † Results from ref. 5.

Phosphate was therefore unlikely to be causing co-precipitation. Further, rubber seed and wheat starch have little phosphate. Although the purity of the thymol-amylose complex was independent of the length of time of dispersion of the starch for up to 2 hr. (*i.e.* the usual conditions for fractionation), the polysaccharide could be residual undispersed granular particles. These might disperse in the more dilute conditions of the recrystallisation. This will be discussed further below.

Although a component with properties intermediate between those of amylose and amylopectin (*e.g.*, an amylopectin with external chains of sufficient length to form complexes with thymol and other reagents) might be expected,[1] "thymol-amylopectin" is not such a molecule. On the basis of β-amylolysis limits, the external chain length is only 9—11 anhydroglucose units compared with 15—16 in amylopectin. Erlander [10] has suggested that glycogen may be a precursor for the synthesis *in vivo* of amylopectin, but although the chain length of the polysaccharide approaches that for glycogen, its physical behaviour is inconsistent with this concept. (It is to be noted that on subfractionation of the polysaccharide, fractions 1C and 1D showed no variation in chain length and β-limit, which may indicate that the polysaccharide is not a mixture of amylopectin and glycogen.) The limiting viscosity number of *ca.* 180 is little different from that for amylopectin (whereas the value for glycogen [11] is *ca.* 10). The relatively low limiting viscosity number suggests that a molecule of "herring-bone" type of structure (*i.e.*, a main chain with side chains of *ca.* 15 glucose units) is unlikely. Rather would the polysaccharide appear to be degraded amylopectin. It is not thought that the difference in internal chain lengths of 5—6 glucose units for the polysaccharide compared with 7—8 units for amylopectin is significant.

The molecular weight of the "thymol-amylopectin" cannot be accurately determined. Ultracentrifugal examination showed that the properties of both the initial amylose-thymol complex and the corresponding "thymol-amylopectin" varied with the variety of potato starch. The initial thymol complex was not always homogeneous (cf. ref. 4).

[10] Erlander, *Enzymologia*, 1958, **19**, 273.
[11] Bryce, Greenwood, and Jones, *J.*, 1958, 3845.

The isolated " thymol-amylopectin " showed a small but variable amount of rapidly sedimenting material—probably amylopectin; estimates of the amount of the latter are made difficult by the Johnston–Ogston effect.[12] However, unpublished light-scattering experiments by Mr. I. G. Jones have indicated that the dissymmetry and the molecular weight (*ca.* 10^8) of " thymol-amylopectin " were of the same order as those of the parent amylopectin.

It is suggested that " thymol-amylopectin " could be amylopectin which has undergone enzymic modification—either by premature cessation of synthesis, or by degradation. As amylopectin is mainly on the outside of the granule,[13] any enzymically-modified material might be associated with residual " granular sacs." The material may be therefore an inherent part of the granule, but the amount and the molecular properties will depend entirely on the botanical environment of the source of the starch.

The authors thank Professor E. L. Hirst, C.B.E., F.R.S., for his interest and helpful comments, the Rockefeller Foundation for financial support, and the Department of Scientific and Industrial Research for a maintenance grant (to W. B.).

THE UNIVERSITY, EDINBURGH, 9. [*Received, April 30th*, 1959.]

[12] Johnston and Ogston, *Trans. Faraday Soc.*, 1946, **42**, 789.
[13] Cowie and Greenwood, *J.*, 1957, 2658.

---

694. *The Infrared Spectra of Some Compounds containing the Trifluoromethylthio-group,* $CF_3{\cdot}S{\cdot}$.

By S. N. NABI and N. SHEPPARD.

The infrared spectra of $CF_3{\cdot}S{\cdot}S{\cdot}CF_3$, $CF_3{\cdot}SCl$, $CF_3{\cdot}S{\cdot}S{\cdot}C_2H_5$, $(CF_3{\cdot}S)_3P$, and $(CF_3{\cdot}S)_2PH$ in the region 4000—400 cm.$^{-1}$ are presented and analysed. Characteristic frequencies of the trifluoromethylthio-group, $CF_3{\cdot}S{\cdot}$, are listed.

IN this paper we discuss the infrared spectra of a series of molecules containing the $CF_3{\cdot}S{\cdot}$ group. Examples are included in which the trifluoromethyl–sulphur group is attached to sulphur, chlorine, or phosphorus atoms. We first interpret a series of absorption bands that are common to the whole series of molecules and are, therefore, associated specifically with the $CF_3{\cdot}S{\cdot}$ group; other features in the spectrum of the individual molecules will then be discussed. Three typical spectra are shown in the Figure.

(*A*) *Characteristic Absorption Bands of the* $CF_3{\cdot}S{\cdot}$ *Group.*—All the compounds studied have prominent bands in the regions 1205—1155, 1135—1095, 765—750, 570—540, and 495—445 cm.$^{-1}$; these are listed in the Table (together with some less prominent, but persistent, overtone and combination bands) where they are compared with the closely analogous frequencies of CF_3Cl. The spectrum of trifluoromethyl chloride has been analysed in detail with the help of band contours in the infrared spectrum and polarisation measurements of the Raman lines.[1,2] It can, therefore, be used as a reliable guide for the assignments of the characteristic frequencies of the $CF_3{\cdot}S{\cdot}$ group to specific modes of vibration. The regularities in the spectral data are self-evident and the appropriate assignments of the bands to particular vibrations of the $CF_3{\cdot}S{\cdot}$ group are given in the Table. It should be noted, as in the case of CF_3Cl, that there is some mixing of the symmetrical CF_3 deformation and C–S (C–Cl) stretching modes of vibration. The frequencies of the $CF_3{\cdot}S{\cdot}$ group in the spectrum of $CF_3{\cdot}S{\cdot}S{\cdot}CF_3$ have been discussed previously by

[1] Plyler and Benedict, *J. Res. Nat. Bur. Stand.*, 1951, **47**, 2245.
[2] Edgell and May, *J. Chem. Phys.*, 1954, **22**, 1808.

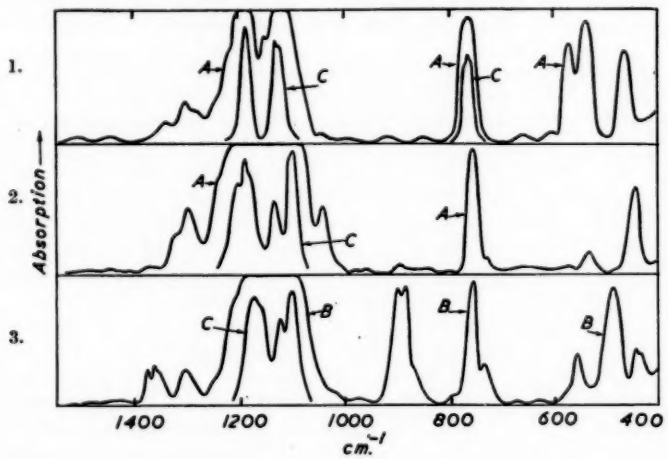
Characteristic frequencies in infrared spectra of $CF_3 \cdot S \cdot$ *groups compared with those of* CF_3Cl.

Vibrational assignments	Frequencies (cm.$^{-1}$)					
	CF_3Cl *	$CF_3 \cdot SCl$	$CF_3 \cdot S \cdot S \cdot CF_3$	$CF_3 \cdot S \cdot S \cdot C_2H_5$	$(CF_3 \cdot S)_3P$	$(CF_3 \cdot S)_2PH$
C–F stretch (asym), ν_4	1212	1189	1205 1109	1158	1180 1170	1177
C–F stretch (sym), ν_1	1104	1133	1133 1095	1117	1127 1095	1125 1103
CF_3 deform (sym), ν_2	782	764	755	750	755	755
CF_3 deform (asym), ν_5	562	570	540	543	560	558
C–S (C–Cl) stretch, ν_3	474	468	447	452	487	492
CF_3 rock, ν_6	356	← Region not investigated →				
$2\nu_4$	2417	2360	2400	—	—	—
$\nu_4 + \nu_1$	2315	2310	2290	2275	2260	2285
$2\nu_1$	—	2250	2230	2220	—	—
$\nu_4 + \nu_2$	1984	1948	1943	1960?	1940	—
$\nu_1 + \nu_2$	1887	1885	1887 1854	1870	1885 1850	1860
$\nu_2 + \nu_5$	1335	1305	1300	1285	1318	1302

* Mean values for fundamentals taken from references (1) and (2); overtones and combination frequencies from ref. (1).

Brandt, Emeléus, and Haszeldine [3] and Haszeldine and Kidd.[4] Except for the lower-frequency bands in the potassium bromide region for which more definite experimental data have now been obtained, the earlier assignments agree with the present ones. The

Infrared spectra of 1, $CF_3 \cdot SCl$; 2, $CF_3 \cdot S \cdot S \cdot CF_3$; *and* 3, $(CF_3 \cdot S)_2PH$. *Curves labelled A are for a pressure of 50 mm., those labelled B for 22 mm., and those labelled C for 1 mm., or less in the case of curve* 1.



C–S stretching frequency of the $CF_3 \cdot S \cdot$ group (490 cm.$^{-1}$) may be compared with the value of 708 cm.$^{-1}$ in methanethiol.[5] Although the difference in frequency is considerable, the type of coupling of this vibration with others of the same symmetry is also markedly different in the two cases. For this reason no reliable conclusions on the relative force constants of the bonds can be made without detailed normal-co-ordinate calculations.

(*B*) *Features in the Infrared Spectra of Specific Molecules.*—(1) *Bistrifluoromethyl*

[3] Brandt, Emeléus, and Haszeldine, *J.*, 1952, 2549.
[4] Haszeldine and Kidd, *J.*, 1953, 3219.
[5] Scott and McCullough, *J. Amer. Chem. Soc.*, 1958, **80**, 3554.

disulphide, $CF_3{\cdot}S{\cdot}S{\cdot}CF_3$. Our spectrum (Figure) agrees well with that determined previously,[3,4] except that a previously reported band of medium strength at 1530 cm.$^{-1}$ (6·53 μ) is not present, and a better-defined spectrum has been obtained below 500 cm.$^{-1}$. No additional band is observed in the potassium bromide region of sufficient strength for a confident assignment to be made of the S–S stretching frequency.

(2) *Trifluoromethanesulphenyl chloride*, $CF_3{\cdot}SCl$. Our spectrum (Figure) agrees well with that previously recorded by Kidd [4,6] in the region 4000—650 cm.$^{-1}$. A strong band at 535 cm.$^{-1}$ additional to those listed in the Table can be assigned with confidence to the S–Cl stretching frequency. For comparison, the coupled S–S and S–Cl stretching frequencies of S_2Cl_2 occur at 538, 448, and 438 cm.$^{-1}$ [7] and the S–Cl frequency of $CCl_3{\cdot}SCl$ lies at 532 cm.$^{-1}$.[8]

(3) *Ethyl trifluoromethyl disulphide*, $CF_3{\cdot}S{\cdot}S{\cdot}C_2H_5$. In addition to the bands of the $CF_3{\cdot}S{\cdot}$ group listed in the Table a number of other medium or strong features appear which can be assigned as follows to vibrations of the $C_2H_5{\cdot}S{\cdot}$ group:[5] 2975, 2940, 2890 (C–H stretch); 1462, 1452 (δCH_3 asym. and δCH_2 bend); 1382 (δCH_3 sym.); 1315 (CH_2 twist); 1263 (CH_2 wag); 1045 (CH_3 rock?); 962 (C–C stretch); 643 (C–S stretch). A weak band at 520 cm.$^{-1}$ may represent the S–S stretching frequency but this is less certain.

(4) *Tris(trifluoromethylthio)phosphine*, $(CF_3{\cdot}S)_3P$. In addition to the $CF_3{\cdot}S{\cdot}$ frequencies in the Table a weak shoulder occurs at 467 cm.$^{-1}$ in the potassium bromide region which may be caused by a P–S stretching vibration.

(5) *Bis(trifluoromethylthio)phosphine*, $(CF_3{\cdot}S)_2PH$. The spectrum (Figure) shows additional bands at 2320 cm.$^{-1}$ (weak) and at 894 cm.$^{-1}$ (a doublet of spacing 13 cm.$^{-1}$, strong) which are almost certainly caused by P–H stretching and angle deformation modes of vibration respectively. In dimethylphosphine, $(CH_3)_2PH$,[9] and bistrifluoromethylphosphine, $(CF_3)_2PH$,[10] the P–H stretching frequencies are at 2290 and 2300 cm.$^{-1}$ and the PH deformation frequencies at 1000 and 850 cm.$^{-1}$ (a doublet) respectively. A medium-strength band at 440 cm.$^{-1}$ may represent a P–S stretching vibration frequency in $(CF_3{\cdot}S)_2PH$.

Experimental.—The method of preparation of the compounds is described elsewhere.[4,11] The spectra were recorded by use of a Perkin–Elmer Model 21 double-beam spectrometer with sodium chloride and potassium bromide prisms. The substances were examined as vapours in a 10 cm. cell having either sodium chloride or potassium bromide windows.

We thank Professor H. J. Emeléus, F.R.S., for his interest and encouragement. One of us (S. N. N.) is indebted to the Royal Commission for the Exhibition of 1851 for an Overseas Scholarship and also to the Government of Pakistan for supplementary grants.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, May 8th*, 1959.]

[6] Kidd, Ph.D. Dissertation, Cambridge, 1953.
[7] Bernstein and Powling, *J. Chem. Phys.*, 1950, **18**, 1018.
[8] Ketelaar and Vedder, *Rec. Trav. chim.*, 1955, **74**, 1482.
[9] Beachell and Katlafsky, *J. Chem. Phys.*, 1957, **27**, 182.
[10] Bennett, Ph.D. Dissertation, Cambridge, 1953.
[11] Emeléus and Nabi, forthcoming publication.

XUM

695. *Distribution of Molecular Weights in Some Polyesters and Polypeptides.*

By M. T. Pope, T. J. Weakley, and R. J. P. Williams.

A recently proposed method for the fractionation of high polymers has been used successfully in the analysis of the molecular-weight distribution in polyesters and polypeptides. In the case of the polyesters the distributions found agree with those deduced from the polymerisation kinetics but the agreement is not so convincing for some of the polypeptides.

The essential features of a new method for the fractionation of high polymers have been described.[1] The method requires that two miscible solvents for the polymers, one good and one poor, should be found in which the polymers have a positive temperature coefficient of solubility. As the suitablity of a given pair of solvents depends upon the polymers, we will discuss separately the two polymers which we have studied. The first polymer fractionations to be described are of polyesters prepared by Flory's method.[2]

The dependence on temperature of the solubility of these polymers in a number of solvents was determined by turbidity titration. Some typical results for one of the most

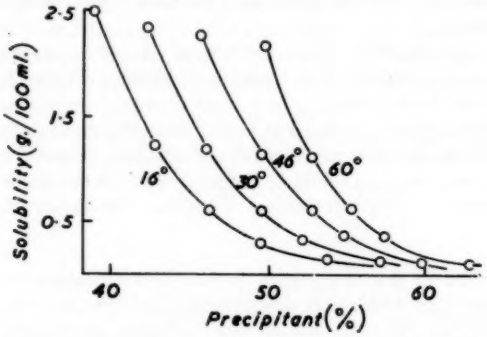


Fig. 1. *The variation of solubility with percentage of precipitant and temperature. Good solvent, ethyl methyl ketone; poor solvent, cyclohexane; molecular weight of polymer,* 1750.

promising solvent systems are shown in Fig. 1. A further requirement of the method [1] is that the solubility of the polymers in the solvents should increase (or decrease) with decreasing (or increasing) molecular weight over the whole range of molecular weight. From the point of view of the fractionation of polyesters then it is inconvenient that the lower-molecular weight members, below about 1000, are decreasingly soluble in non-polar solvents, such as hexane, as the molecular weight decreases, whereas the highest molecular weight polymers are decreasingly soluble in the same solvent as the molecular weight increases. Nor is the order of solubility of fractions of different average chain length simple in polar solvents such as acetone. The suitability of given solvents for fractionation depends then on the average molecular weight of the polymers. We have found that the following solvent systems are most useful:

Number-average molecular weight	Poor solvent	Good solvent
<500(*A*)	Cyclohexane	30% Ethanol in cyclohexane
>500(*B*)	Cyclohexane	30% Ethanol in cyclohexane. Change to ethyl methyl ketone after 20 fractions
>800(*C*)	Cyclohexane	Ethanol. Change to ethyl methyl ketone after 25 fractions
>1,500(*D*)	50% Ethanol–cyclohexane	Ethyl methyl ketone

N.B. No two-solvent system is suitable for analysis in the range M_n = 500—1500.

[1] Baker and Williams, *J.*, 1956, 2352.
[2] Flory, *J. Amer. Chem. Soc.*, 1940, **62**, 1057.

Details of Method

In the analysis of polystyrenes [1] small samples (*ca.* 500 mg.) were put on the column. In the present analyses up to 5·0 g. of polyesters were analysed in a single experiment. This alteration of conditions was enforced by the difficulty of determining the molecular weights of the fractions. The titration method used for the determination of the number-average molecular weights of both whole polymers and fractions is to be described.[3] In all other respects the method was that described.[1]

Results

The efficiency of fractionation of a polymer can be tested in three ways. The first is to refractionate the material and observe the spread in the fractions. It is usual to test the efficiency of any chromatographic procedure in this manner. Fig. 2 illustrates the fractionation of a polyester of number-average molecular weight, $M_n = 2500$, and the refractionation of some sample fractions. It can be seen that the method is satisfactory. A given analysis can be accurately reproduced (Table 1).

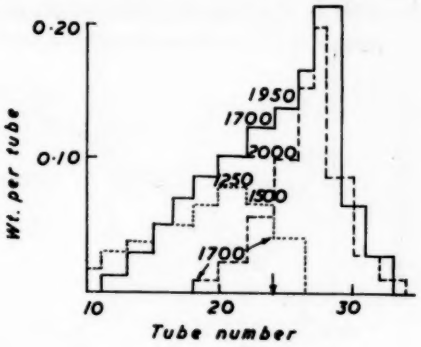


Fig. 2. *The fractionation of a polyester (full line) and the refractionation of two artificial polymers formed from mixing together the first fractions up to tube number 22 and the fractions from this tube number to the end of the chromatogram. Numbers in the Figure refer to molecular weights.*

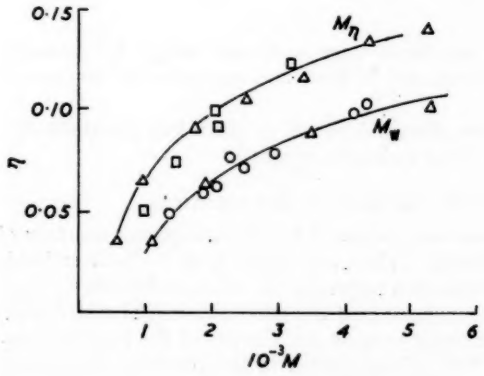


Fig. 3. *M_n and M_w of some whole polymers plotted against intrinsic viscosity, △, compared with M_n for column fractions, ○, and batch fractions, □.*

A second method is to compare those physical properties of the fractions, *e.g.*, bulk and intrinsic viscosity, which depend more nearly on weight-average than number-average molecular weight, with the properties of the bulk polymers. Typical data are in Fig. 3. The properties of the fractions indicate that the ratio of $M_w : M_n$ does not significantly exceed 1·0. The properties of fractions prepared by a conventional fractional precipitation are also given for comparison.

[3] Pope and Williams, *J.*, in the press.

TABLE 1. *Reproducibility of fractionations of polyesters.*

Chromato-gram tube No.	Weight per tube (1)	Weight per tube (2)	M (1)	M (2)	Chromato-gram tube No.	Weight per tube (1)	Weight per tube (2)	M (1)	M (2)
14,15	0·03	0·02	590	590	24,25	0·14	0·14	2150	2420
16,17	0·05	0·04	860	790	26,27	0·19	0·17	2950	3400
18,19	0·075	0·07	990	—	28,29	0·21	0·21	3550	4200
20,21	0·095	0·09	1270	1260	30,31	0·15	0·10	4000	5000
22,23	0·12	0·12	1680	—					

A third method is to determine the distribution of molecular weight in a polymer for which the distribution is well established by kinetic studies. The kinetics of the formation of polyesters of high molecular weight only are sufficiently understood for this purpose.[2,3] An analysis of a high molecular weight polyester is shown in Fig. 4. The full curve was

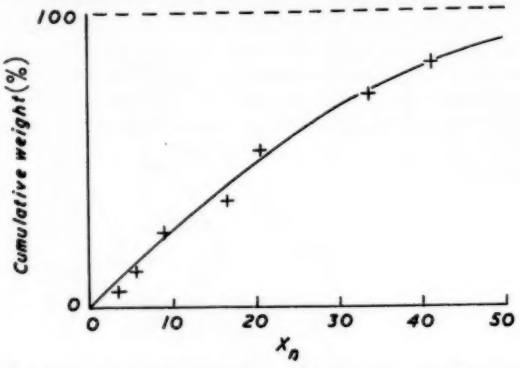


FIG. 4. *The distribution of molecular weight in a high-molecular weight polyester compared with the theoretical distribution given by the full line.*

obtained theoretically from the known number-average molecular weight by assuming the most probable distribution. The agreement is good and supports the method of analysis.

Some analyses of polyesters of unknown distribution will be given in a paper devoted to the kinetics of formation of polyesters of *low* molecular weight.[3]

DISTRIBUTION OF MOLECULAR WEIGHTS IN POLYPEPTIDES

The polypeptides which we will discuss were prepared for us through the courtesy of Dr. C. H. Bamford (Courtaulds, Maidenhead). They were made from cyclic *N*-carbonic anhydrides through the action of (*A*) pre-formed polymers, (*B*) lithium chloride–methylhydantoin, and (*C*) aniline. It has been supposed that the molecular-weight distribution in these polymers is dependent on the initiator because the kinetics of the reaction vary greatly from one initiator to another. For polymerisation in the presence of prepared polymer the polymer has been stated to have a Poisson distribution.[4] The Poisson distribution is extremely narrow as compared with the most probable distribution which is found in polyesters. It was therefore of great interest to see if our method of fractionation could lead to a fractionation of these polypeptides. The lithium chloride–methylhydantoin- and aniline-initiated polymers should have a molecular-weight distribution more nearly like that of the polyesters according to the kinetics, but the actual distribution is complex.[5]

DETAILS OF FRACTIONATION METHOD

The apparatus was as described elsewhere.[1] When we attempt the fractionation of new polymer the only feature that must be changed is the solvent gradient. The solvent gradient used in the fractionation of the polypeptides was produced by using cyclohexane as non-solvent

[4] Ballard and Bamford, *Proc. Roy. Soc.*, 1954, *A*, **223**, 495.
[5] Ballard, Bamford, and Weymouth, *Proc. Roy. Soc.*, 1955, *A*, **227**, 155.

in the mixing vessel, and a mixture of 20% methanol in ethanol as the good solvent in the reservoir. This system was chosen as the polymers showed a positive temperature coefficient of solubility in it and their solubility decreased regularly with increasing molecular weight. The fractions were characterised by a determination of their viscosity in aqueous solution with an Ubbelohde viscometer. The molecular weight of the fractions could then be found by using the expression of Fessler and Ogston.[6] This expression was not likely to be greatly in error for fractions of high homogeneity as the expression itself was obtained empirically from a study of polymers having a Poisson distribution. (The results below confirmed this distribution for the particular polymers used by Fessler and Ogston for their calibration.)

Results

Fig. 5 shows the analysis of an artificial mixture of two polymer-initiated polypeptides of specific viscosity 0·051 and 0·075 in 0·5% solution. Not only has there been a separation of the two polymers but there is also a fractionation within each polymer. Fig. 6 gives the

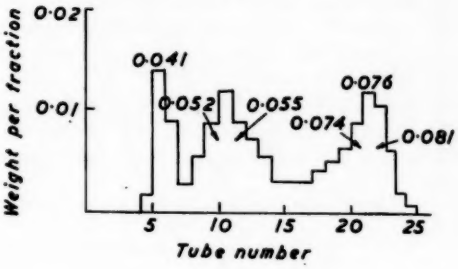


FIG. 5. *The fractionation of a mixture of two polysarcosines. The three concentration peaks imply no more than that the polymer is fractionated. Numbers refer to specific viscosity.*

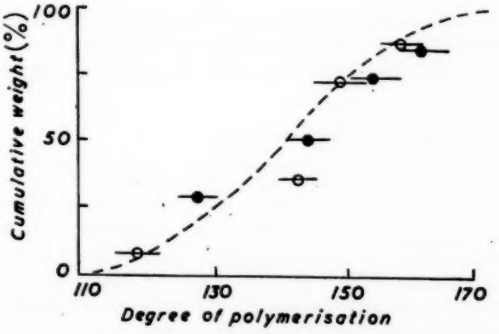


FIG. 6. *Distribution of molecular weights in a polysarcosine compared with the Poisson distribution.*

distribution of molecular weight in one of the polymers. It was obtained from two analyses. The broken line is a calculated distribution from the known molecular weight of the polymer, a distribution according to the Poisson equation being assumed.[7] There can be little doubt that this equation correctly represents the distribution. These observations add further strength to the postulated kinetic scheme.

The kinetics of the lithium chloride–methylhydantoin-initiated polymerisation of *N*-carbonic anhydrides lead to a very complex distribution function.[5] We analysed polymers prepared in this way with the result shown in Fig. 7. The distribution is certainly narrower than that calculated on the kinetic scheme suggested [5] but is not quite so narrow as in the pre-formed polymer-initiated polymers. Because of the discrepancy between the kinetically determined and observed distributions a further sample of lithium chloride–methylhydantoin-initiated polymer was prepared under very carefully controlled conditions

[6] Fessler and Ogston, *Trans. Faraday Soc.*, 1951, **47**, 667.
[7] Flory, " Principles of Polymer Chemistry," Cornell Univ. Press, New York. 1953, 337.

XUM

by Dr. Bamford, and this polymer was analysed by the column method. It was again shown to have a narrow distribution very much as in Fig. 7 in which $M_w : M_n$ did not exceed 1·2. (As we observed no very low molecular weight material we concluded that it was absent.) The distribution suggested for this polymer from the kinetics should have a ratio $M_w : M_n$ in the region of 2·0.[5] The discrepancy between the observations is so large that additional checks were attempted on the $M_w : M_n$ ratio by measuring the number-average molecular weight of the polymer by two methods: (*a*) from the osmotic pressure of the polymer in chloroform solution and (*b*) from the number of basic end-groups. In chloroform the osmotic head did not give a steady equilibrium value but fell slowly. This showed that some polymer was diffusing through the membrane and the method cannot be considered to be very reliable. However the fall in the head was sufficiently gradual

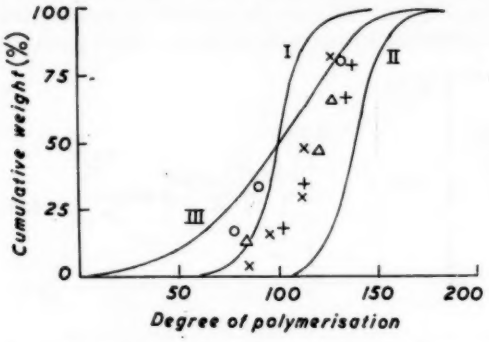


FIG. 7. *Distribution of molecular weights in a* LiCl–*hydantoin-initiated polymerisation of sarcosine* (three separate experiments) *compared with two Poisson distributions* I *and* II *and the distribution suggested* [5] *for such polymers* (III).

to permit extrapolations to zero time. The number-average molecular weights obtained by extrapolation to infinite dilution, which may be too high, are given in Table 2 where the molecular weights from other methods are also given. $M_w : M_n$ is close to 1·2 and is certainly not larger than this.

TABLE 2. *Molecular weights of polysarcosines.*

Initiator		Viscosity	Osmotic	End group
Preformed polymer	(*a*)	7100	—	—
	(*b*)	10,300	—	—
LiCl–Methylhydantoin	(*c*)	6750	5500	5700
	(*d*)	7470	—	7500
Aniline	(*e*)	7100	Method failed	6750
	(*f*)	8300	,,	7300

The position of travel of the polymer in the chromatograms indicates that all the polymers have very similar molecular weights except (*b*) which is obviously much higher.

A sample of polysarcosine was next prepared by aniline initiation. A broad distribution was expected from the kinetics but the determined distribution was again closer to the Poisson distribution than any other. Confirmation of the distribution is provided by the molecular weights in Table 2. It appears that all the synthetic polysarcosines prepared from *N*-carbonic anhydrides have narrow distributions.

In conclusion we comment that the fractionation achieved in the analyses of the polypeptides is a separation of polypeptides which differ in molecular weight by about 10%. It may well be that a similar technique will fractionate natural peptides in the same molecular-weight range, approximately 10,000, and having similar differences in molecular weight.

One of us (M. T. P.) is indebted to Courtaulds Scientific and Educational Trust Fund for a Scholarship. We have had advice and assistance from Dr. C. H. Bamford.

INORGANIC CHEMISTRY LABORATORY, OXFORD. [*Received, January 6th,* 1959.]

696. *The Spectrum of the Coronene Crystal.*

By L. E. Lyons and J. R. Walsh.

First-order calculations of transition energies and oscillator strengths in the spectrum of the coronene crystal, using known data of crystal structure and the spectrum of the solution, are made.

Coronene is a molecule of interest theoretically because it has a similar symmetry to that of benzene and yet the spectrum lies in a more convenient region than does that of benzene. No work has been reported on the spectrum of its crystal and so additional interest attaches to calculations of certain of its spectral properties. The experiments when done will then serve as a check on the theory and its basic assumptions. The theoretical methods used here are similar to those developed and used previously.[1-4] The theory has already met with some success,[5-7] but has not previously been applied to coronene. It should be noted that the application to coronene is limited to a certain extent by the use of the dipole term only in the series expansion of the interaction between molecules. However, this limitation should be little greater than in the case of anthracene where the theory works satisfactorily.[1,7]

The detailed crystal structure of coronene has been determined.[8] The crystal is monoclinic prismatic, the space group $P2_1/a$, and there are two planar centro-symmetric molecules in a unit cell. The position of one molecule can be transformed into that of the

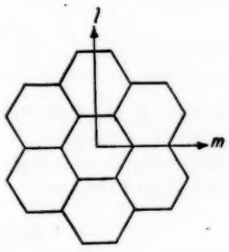


Fig. 1. *Directions in the coronene molecule.*

other by a translation through $b/2$ followed by a reflection in the ac plane and a translation through $a/2$. Molecular directions in the second molecule are therefore related to directions in the first molecule by this transformation. The unit cell dimensions are $a = 16{\cdot}10 \pm 0{\cdot}05$; $b = 4{\cdot}695 \pm 0{\cdot}005$; $c = 10{\cdot}15 \pm 0{\cdot}05$ Å; $\beta = 110{\cdot}8° \pm 0{\cdot}2°$. Direction cosines relating crystal and molecular directions are $la = 0{\cdot}0912$; $lb = 0{\cdot}0765$; $lc' = 0{\cdot}9928$; $ma = 0{\cdot}7174$; $mb = 0{\cdot}6865$; $mc' = -0{\cdot}1188$; $na = -0{\cdot}6905$; $nb = 0{\cdot}7233$; $nc' = 0{\cdot}0078$, where c' is perpendicular to a and b. In the coronene molecule the longer in-plane axis is denoted by l, the shorter by m (see Fig. 1).

X-Ray evidence has shown that in the crystal the coronene molecule displays hexagonal symmetry although the various carbon–carbon bonds range in length from 1·385 to 1·430 Å. The appropriate symmetry group for the molecule is thus D_{6h}.

The spectrum [9] of the coronene solution between 28,000 and 34,000 cm.$^{-1}$ shows three transitions, I, II, and III, which bear a striking resemblance to those in benzene, having oscillator strengths, f, of I, 0·003; II, 0·24; III, 0·6. Transition III, which has a fairly

[1] Craig and Hobbins, *J.*, 1955, 539.
[2] Lyons, *J.*, 1958, 1347 and references therein.
[3] Craig and Walsh, *J.*, 1958, 1613.
[4] Lyons, Walsh, and White, *J.*, 1959, in the press.
[5] Craig and Hobbins, *J.*, 1955, 2309.
[6] Lyons, *J. Chem. Phys.*, 1955, **23**, 1973.
[7] Lyons and Morris, *J.*, 1959, 1551.
[8] Robertson and White, *Nature*, 1944, **154**, 605; *J.*, 1945, 607.
[9] Clar, "Aromatische Kohlenwasserstoffe," Springer, Berlin, 1941.

XUM

sharp peak at about 32,800 cm.$^{-1}$, is presumably allowed, and the symmetry of the upper electronic state is therefore E_{1u}. In so far as the analogy with benzene is followed, transitions I and II are allowed by vibrational or other perturbation. In the free-electron terminology the upper states of transitions are described as I, ^1L_b; II, ^1L_a; III, ^1B_b.

In the application of the theory to coronene, attention was confined to excited states having the excitation wave-vector equal to zero. Wave functions which transform as irreducible representations of the factor group are:

$$\gamma^{\alpha(\beta)} = (1/\sqrt{2})\,(\phi_{\mathrm{I}} \pm \phi_{\mathrm{II}})$$

where α is to be read with the plus sign, β with the minus; subscripts I and II refer to the sites of a unit cell; ϕ refers to a product of molecular wave functions when one molecule of the crystal is excited to an E_{1u} degenerate level. In this case the solution of the Schrödinger equation leads to the secular equation

$$\begin{vmatrix} x + \mathscr{J}_\alpha{}^{ll} & \mathscr{J}_\alpha{}^{lm} \\ \mathscr{J}_\alpha{}^{lm} & x + \mathscr{J}_\alpha{}^{mm} \end{vmatrix} \begin{vmatrix} x + \mathscr{J}_\beta{}^{ll} & \mathscr{J}_\beta{}^{lm} \\ \mathscr{J}_\beta{}^{lm} & x + \mathscr{J}_\beta{}^{mm} \end{vmatrix} = 0 \quad . \quad (1)$$

where $x = w + D - E$; w denotes the energy of excitation of an isolated molecule; $D = \sum_{i \neq j} \int (\phi_i' \phi_j V_{ij} \phi_i' \phi_j - \phi_i \phi_j V_{ij} \phi_i \phi_j) \mathrm{d}\tau$; ϕ_i' refers to the excited state of molecule i; E is the energy of excitation in the crystal:

$$\mathscr{J}_{\alpha(\beta)}{}^{ll} = \sum I_{\mathrm{I}}{}^{ll} \pm \sum I_{\mathrm{II}}{}^{ll}$$
$$\mathscr{J}_{\alpha(\beta)}{}^{lm} = \sum J_{\mathrm{I}}{}^{lm} \pm \sum J_{\mathrm{II}}{}^{lm}$$

I and II denote the sites in the unit cell. Again, α is to be read with the plus sign on the right hand side, β with the minus.

$\sum I_{\mathrm{I}}{}^{ll}$ refers to the sum over molecules on sites of type I.

I^{ll} refers to an integral of the type

$$\int \phi_i{}^l \phi_i V_{ij} \phi_j{}^l \phi_j \,.\, \mathrm{d}\tau$$

where $\phi_i{}^l$ is the wave function which is the lth component of the degenerate excited state of the molecule (see 3).

ϕ_j is the wave function of the jth molecule in its ground state. J^{lm} differs from I^{ll} only in that one of the superscripts l is replaced by m.

The choice of the in-plane axes as l and m has been shown [3] to be permissible.

Interactions between inequivalent molecules were calculated on the dipole–dipole approximation and are given in Table 1, where the molecules are designated as in Fig. 2.

TABLE 1. *Interactions* (cm.$^{-1}$ Å^{-2}) *between inequivalent molecules separated by less than* 20 Å.

Same (001) plane			Adjacent (001) plane		
Molecule paired with *O*	$l-l$	$m-m$	Molecule paired with *O*	$l-l$	$m-m$
C, D, E, or F	190	−251	*C′ or D′*	−14	−19
G, L, S, M	90	−19	*G′, L′*	5	−16
U, T, V, W	40	22	*U′, V′*	2	3
I, J, P, Q	8	−12	*F′, E′*	−105	−33
H, K, N, R	7	−9	*S′, M′*	−31	8
X_1, X_2, X_3, X_4	6	−6	*T′, W′*	−1	22
Y_1, Y_2, Y_3, Y_4	2	−3	*Q′, N′*	•	•
Total interaction in one (001) plane (up to 20 Å)	1366	−1111		−288	−70

The means of intermolecular interactions on the same approximation are listed in Table 2. Those for the complete crystal were obtained by the Ewald–Kornfeld method and include

TABLE 2. *Sum of intermolecular interactions.*

Interaction type	Equivalent molecules	Inequivalent molecules	Interaction type	Equivalent molecules	Inequivalent molecules
l–l	1971	508 (790 *)	*l–n* }	−678	295
m–m	−828	−902 (−1251 *)	*n–l* }		
n–n	−1145	−978	*n–m* }	−3691	260
l–m }	−31	−443	*m–n* }		
m–l }					

* Denotes sum up to 20 Å radius. Other figures refer to complete crystal.

cross terms, *i.e.*, terms of the type *l–m* and are given for sets of both equivalent and inequivalent molecules. It is seen from Table 2 that the error from limiting the summation to a sphere of 20 Å radius, although not overwhelming, is appreciable.

The solutions to (1) are

$$E_\alpha = w + D + (\mathscr{J}_\alpha^{ll} + \mathscr{J}_\alpha^{mm})/2 \pm (1/2)\{(\mathscr{J}_\alpha^{ll} - \mathscr{J}_\alpha^{mm})^2 + 4(\mathscr{J}_\alpha^{lm})^2\}^{1/2}$$

with a similar expression for the β state.

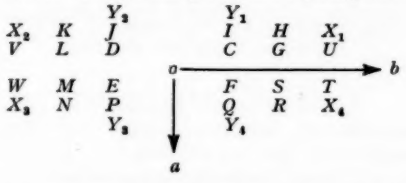
Numerical values were calculated and are given in Table 3, in units of cm.$^{-1}/M^2$, where M denotes the transition moment.

TABLE 3. *Calculated positions of crystal levels for $k = 0$ relative to $w + D$.*

α (*ac* polarized)	2533	−1783
β (*b* polarized)	1576	−39

The polarizations of the four transitions to γ^α and γ^β were obtained by a consideration of the factor group, C_{2h}. When subjected to the operations of this group, γ^α behaved as a

FIG. 2. *Designation of sites in the* (001) *plane.*



reducible representation, $B_u + B_u$. Therefore there are expected in the spectrum two transitions, each polarized in the *ac* plane. From γ^β there are expected two further transitions, each polarized *b*.

The intensity of the solution transition will be divided in the crystal amongst the four components. The total intensity along the three crystal directions, *a*, *b*, and *c'*, was calculated from the direction cosines relating the molecular and crystal directions as

$$I_a : I_b : I_{c'} = 1{\cdot}10 : 1{\cdot}00 : 2{\cdot}10$$

The total intensity along each crystal direction will be divided in each case between the two components of similar polarization. The method described previously [3] was used to show that in *a* polarization the ratio of the intensity of one component to that of the other will be only (1/5900). Similarly, in *c'* polarization, the ratio is (32,000/1) and in *b* polarization 1/6·3. In a given crystal therefore only one of the *a* components is likely to be observable, and one of the *c'* components, although both of the *b* components should appear. The weaker *a* component is that of lower energy, the weaker *c'* component that of higher energy. Both *a* and *c'* components appear at the same energies.

The crystal spectrum has not yet been observed but may now be predicted. It is necessary to assume the oscillator strength of the transition in solution. This was taken

as $f = 1{\cdot}52$, corresponding to $M = 1{\cdot}46$ Å. The predicted spectrum is shown in Fig. 3 and Tables 4 and 5.

The " Davydov " splitting is the difference between oppositely polarized components arising from a molecular transition of given polarization. For l and m polarized molecular transitions the Davydov splittings were calculated as 957 and -1744 cm.$^{-1}/M^2$. On using a simpler approach, in which coronene is considered in the group D_{2h}, the Davydov

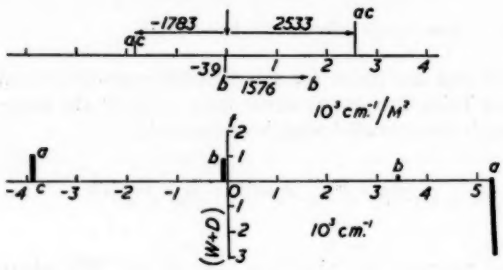


FIG. 3. *Predicted band positions in the crystal. Upper: for unit transition moment. Lower: for* $M = 1{\cdot}46$ Å *concentrated at one frequency. f denotes the oscillator strength. a, b, c denote the polarization of the bands.*

splittings were 1580 and -2502 cm.$^{-1}/M^2$. The fuller more accurate treatment therefore shows that, although the simpler treatment gives the correct sizes and order of magnitude for the splitting yet it should be corrected by about -30%.

TABLE 4. *Energies of transitions in the crystal corresponding to the* 33,130 *cm.*$^{-1}$ *transition in the free molecule.*

α (*ac* polarized)		β (*b* polarized)	
38,530 cm.$^{-1}$	2597 Å	36,494 cm.$^{-1}$	2740 Å
29,337	3412	33,052	3026

TABLE 5. *Values of f calculated for crystal transitions corresponding to* 33,130 *cm.*$^{-1}$ *transition in the free molecule.*

	α		β
	a polarized	*c* polarized	*b* polarized
Higher-frequency component	0·0002	2·67	0·17
Lower frequency component	1·06	0·00006	0·94

Total *f* value in crystal = 4·84.

Whilst the present theory in the form used in this paper is correctly applied to molecular transitions which are allowed and therefore intense, it is none the less possible to make at least qualitative remarks about the other transitions. In particular the upper state of transition II in benzene has been assigned $^1E_{2g}$ [10] and $^1B_{1u}$,[11] and is presumably similar in coronene.

Coronene crystal forces should produce four components in the case of the E_{2g} assignment and two components in the case of B_{1u}. A complete analysis of a well-resolved crystal spectrum should therefore enable a decision between the alternatives to be made. The magnitude of the splitting in both cases is expected to be much smaller than for the allowed transition due to the necessary presence of vibrations. Experiments on the spectrum of the crystal are being conducted. All predictions are subject to the limitations discussed elsewhere.[4]

We acknowledge the helpful support granted by I.C.I.A.N.Z. Pty. Ltd. to one of us (J. R. W.).

DEPARTMENT OF PHYSICAL CHEMISTRY,
THE UNIVERSITY OF SYDNEY.

[*Received, February* 13*th*, 1959.]

[10] Dunn and Ingold, *Nature*, 1955, **176**, 65.
[11] *E.g.*, Goeppart-Meyer and Sklar, *J. Chem. Phys.*, 1938, **6**, 645.

697. *A Theoretical Treatment of the Chemistry of Quinoline.*

By R. D. Brown and R. D. Harcourt.

Extensive calculations by the simple Hückel molecular-orbital method are reported for quinoline and some related systems. They lead to an interpretation of many of the chemical properties of quinoline and especially of the variety of orientations displayed under different conditions of electrophilic substitution. Some mechanisms are tentatively suggested for several reactions of quinoline.

The values of the Hückel parameters found necessary for interpreting the chemistry of quinoline agree with values found in studies on other related heterocyclic systems.

The simple Hückel molecular-orbital method has been able to account for some of the main features of heterocyclic chemistry,[1-3] especially when, more recently, a possible plurality of mechanism of electrophilic substitution arising from protonation or deprotonation of heteroatoms was considered.[4,5] In the present paper a detailed correlation of the chemistry of quinoline with Hückel molecular-orbital calculations is presented. Previous molecular-orbital treatments of quinoline [2,6,7] have been successful in explaining some of the chemistry, but the present study offers an interpretation of a wider range of reactions and especially of some of the finer details of electrophilic substitution which have recently been revealed.[5,8-10] In the case of almost every reaction discussed in the ensuing analysis there is no detailed mechanistic evidence available; we have had to assume plausible mechanisms, and one outcome of the present study has been the proposing of mechanisms for several reactions, based mainly on theoretical data.

Another purpose of the present study was to provide more information on the molecular-orbital parameters. It was of interest to see if the values of the parameters which are needed to account for the chemistry of quinoline are in accord with recent estimates of parameters by the V.E.S.C.F. method [11,12] and with some Hückel molecular-orbital studies of other heterocycles.[13]

Details of Calculations

The appropriate values of the coulomb parameter h for nitrogen ($\alpha^0_N = \alpha^0 + h\beta^0$) * in the Hückel molecular-orbital treatment of quinoline and the quinolinium cation (the nitrogen core in these conjugated systems presenting charges of $+1$ and $+2$ respectively to the π-electron cloud) may be roughly established from the results of more elaborate theoretical studies of pyridine [12,14,15] and of pyrrole.[16] For a core charge of $+1$, values of h in the range 0·2—0·5 have been found; we have therefore selected $h = 0{\cdot}5$ to represent nitrogen of core charge $+1$ when studying the variation of other parameters for constant h. In the quinolinium cation

* The superscript zero's are used with the symbols designating coulomb and resonance integrals to indicate that Hückel molecular-orbital quantities are being considered, The symbols α and β are used, with somewhat different meanings, in more elaborate calculations on π-electron systems.

[1] Wheland and Pauling, *J. Amer. Chem. Soc.*, 1935, **57**, 2086.
[2] Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87.
[3] Longuet-Higgins and Coulson, *J.*, 1949, 971; Brown and Heffernan, *Austral. J. Chem.*, 1956, **9**, 83.
[4] Bassett and Brown, *J.*, 1954, 2701; Brown and Heffernan, *J.*, 1956, 4288.
[5] Brown, "Current Trends in Heterocyclic Chemistry," Butterworths, London, 1958, p. 13.
[6] Sandorfy and Yvan, *Bull. Soc. chim. France*, 1950, **17**, 131.
[7] Dewar and Maitlis, *J.*, 1957, 2521.
[8] Dewar and Maitlis, *J.*, 1957, 944.
[9] Brown, unpublished experiments (preliminary report of some results in ref. 5).
[10] de la Mare, Kiamud-Din, and Ridd, *Chem. and Ind.*, 1958, 361.
[11] Brown and Heffernan, *Trans. Faraday Soc.*, 1958, **54**, 757.
[12] Brown and Heffernan, V.E.S.C.F. results for pyridine in course of publication.
[13] Brown and Coller, *Austral. J. Chem.*, 1959, **12**, 152.
[14] Brown and Heffernan, *Austral. J. Chem.*, 1957, **10**, 211.
[15] McWeeny and Peacock, *Proc. Phys. Soc.*, 1957, **70**, *A*, 41; Nishimoto and Mataga, *Z. phys. Chem.*, 1957, **12**, 335.
[16] Brown and Heffernan, *Austral. J. Chem.*, 1959, **12**, 319.

XUM

values of h around 2·0 should be appropriate as judged from the study of pyrrole and related compounds.[13,16]

It is also possible to decide in advance the approximate magnitude of the auxiliary inductive coulomb parameter h' for the carbon atoms adjacent to nitrogen. For the quinolinium cation a value near 0·25 should be appropriate since both direct theoretical studies of pyrrole [16] and an analysis of the chemistry of pyrrole, indole, and carbazole [13] indicate this value when the nitrogen has a core charge of +2. To account for the chemistry of quinoline it seems necessary to select a slightly smaller value, about 0·2. The value of the auxiliary parameter for the free base should be less than this because there is now good evidence [12,16] that the auxiliary inductive effect arises largely from core attraction effects, and nitrogen of core charge +1 will clearly have less effect on adjacent carbon atoms than will nitrogen of core charge +2. Theoretical studies of pyridine [12,14] indicate a value rather less than 0·1. The present analysis of the chemistry, with $h = 0{\cdot}5$, requires h' to lie in the range 0·07—0·09, and the value $0{\cdot}08_5$ seems to be most appropriate.

The CN resonance integral β^0_{CN} has for simplicity been taken to have the standard value β^0. To test the sensitivity of the results to the value of this integral the charge densities for quinoline were also calculated * for $\beta^0_{CN} = 1{\cdot}1\beta^0$. The results, shown in Table 1, reveal that the π-electron densities are insensitive to the value assumed for β^0_{CN}. This is not surprising because quinoline may be regarded as a slightly perturbed alternant hydrocarbon, and for the latter the atom-bond polarizabilities are identically zero.[17] The value adopted in this work for β^0_{CN} is also supported by the V.E.S.C.F. calculations on pyridine.[12,14]

TABLE 1. *Variation of π-electron densities of quinoline with* β^0_{CN}. ($k = \beta^0_{CN}/\beta^0$ with values for $h = 0{\cdot}5$, $h' = 0$).

Position	$k = 1{\cdot}0$	$k = 1{\cdot}1$	Position	$k = 1{\cdot}0$	$k = 1{\cdot}1$
1	1·2159	1·1940	6	1·0029	1·0028
2	0·8961	0·9049	7	0·9840	0·9861
3	1·0084	1·0079	8	1·0125	1·0122
4	0·9318	0·9404	9	0·9566	0·9588
5	0·9884	0·9901	10	1·0016	1·0016

Localization energies, especially for the 2-position, are more sensitive to the value adopted for β^0_{CN} than are the π-electron densities (compare Figs. 6—7, 9—10, 14—15). However, an acceptable correlation of theory and experiment is found in the present analysis over a range of physically reasonable values of this resonance integral.

The values of electrophilic and radical localization energies for the 2-position are more uncertain than those for other positions when the auxiliary inductive parameter is used because it is not clear what energy should be assigned to the electrons localized at the position of attack.[18] We have used the value $\alpha^0 + h'\beta^0$ for such electrons whereas Wheland,[18] who included the overlap integral, used $\alpha^0 + 0{\cdot}75h'\beta^0$. It is possible that our electrophilic and radical localization energies unduly favour the 2-position. Fortunately the 2-position plays an important part in our analysis only for attack by nucleophiles, and this uncertainty does not enter for nucleophilic localization energies.

The plan of the calculations was to cover all reasonable values of h and h' to rule out the possibility of attributing any discrepancy between theory and experiment to an inappropriate choice of these coulomb parameters. To make it easy to assess how each theoretical quantity (π-electron density or localization energy) will alter when different values of h and h' are selected, the theoretical results are presented in graphical form as follows: First, the quantity is plotted as a function of h for a constant value of h' (the value of zero for h' is convenient; a corresponding graph for any other constant value of h' up to, say, 0·5 can be estimated by linear interpolation if necessary by using data from the graph with h' as abscissa). Then the quantity is plotted as a function of h' for constant h, values being chosen which are thought to be near the optimum values for the conjugated systems under discussion (usually quinoline and quinolinium). These graphs make it possible to estimate readily the values of the theoretical quantities for any other reasonable value of h and h' by linear interpolation.

* Our results were mostly obtained on the Melbourne University computer C.S.I.R.A.C. and it was more convenient to calculate two separate sets of π-electron densities than to re-programme the computer for calculating atom-bond polarizabilities directly.

[17] Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1947, *A*, **192**, 16.
[18] Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900.

Results and Discussion

Attack by Nucleophiles.—It is convenient to start by considering some reactions of quinoline and its derivatives which involve attack by nucleophiles because our analysis of these reactions has bearing on other reactions considered below.

Fig. 1. *π-Electron densities of quinoline as a function of h for h′ = 0.*

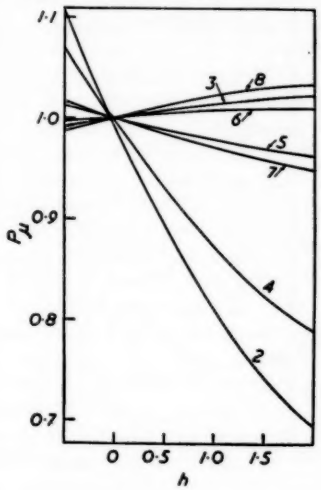


Fig. 2. *π-Electron densities of quinoline (h = 0·5) as a function of the auxiliary inductive parameter.*

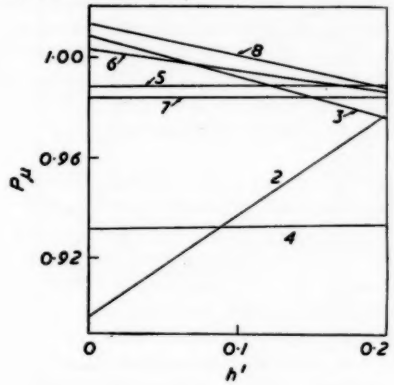


Fig. 3. *Nucleophilic localization energies of quinoline as a function of h for h′ = 0.*

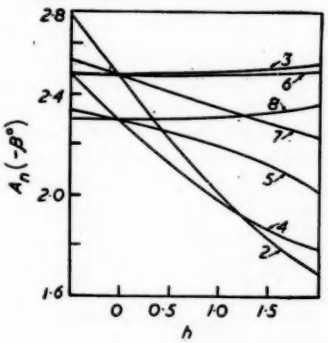
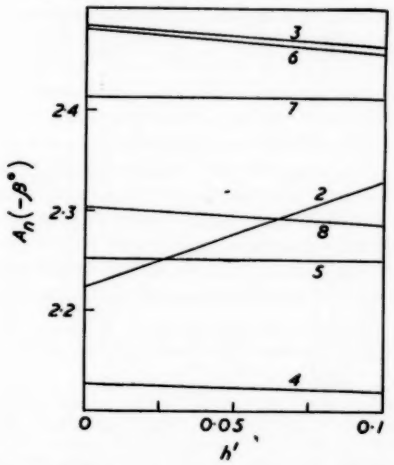


Fig. 4. *Nucleophilic localization energies of quinoline (h = 0·5) as a function of the auxiliary inductive parameter.*



In the amination of quinoline in liquid ammonia it is possible that the reaction takes place between a quinoline molecule and an amide anion. The order of reactivity of quinoline positions towards the nucleophile is unambiguously 2 > 4 > others.[19] Since the reaction occurs readily it would be expected [5,20,21] that the orientation of attack would tend to be correlated with the π-electron distribution (Figs. 1 and 2) rather than with

[19] Bergstrom, *J. Amer. Chem. Soc.*, 1934, **56**, 1748.
[20] Hammond, *ibid.*, 1955, **77**, 334.
[21] Bassett, Brown, and Penfold, *Chem. and Ind.*, 1956, 892.

nucleophilic localization energies (Figs. 3 and 4). It is evident from Fig. 2 that the experimental observations can be correlated with the π-electron densities of the quinoline

FIG. 5. *π-Electron densities of quinolinium ($h = 2$) as a function of the auxiliary inductive parameter.*

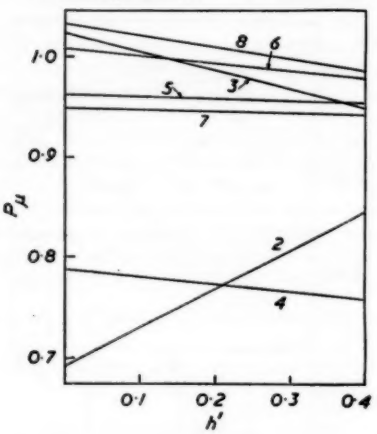


FIG. 6. *Nucleophilic localization energies of quinolinium ($h = 2$, $\beta^0_{CN} = \beta^0$) as a function of the auxiliary inductive parameter.*

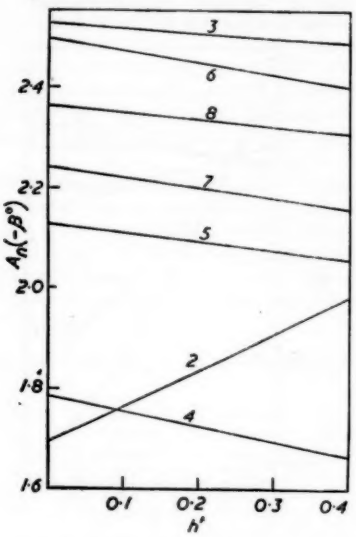


FIG. 7. *Nucleophilic localization energies of quinolinium ($h = 2$, $\beta^0_{CN} = 1{\cdot}2\beta^0$) as a function of the auxiliary inductive parameter.*

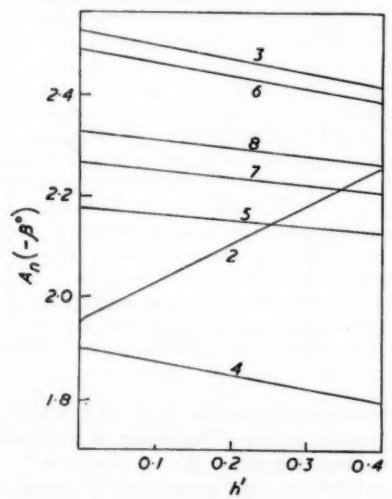
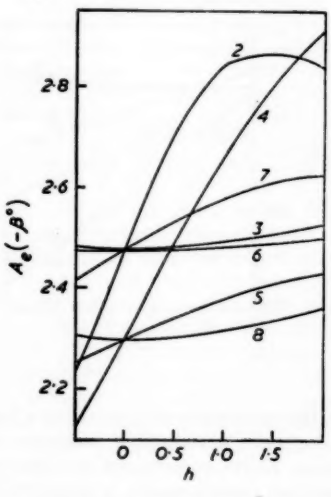


FIG. 8. *Electrophilic localization energies of quinoline as a function of h for $h' = 0$.*



molecule if the auxiliary inductive effect is not too large ($P_2 < P_4$ for $h' < 0{\cdot}090$). However, it is not possible to account for the observations in terms of localization energies for any reasonable values of the Hückel parameters for quinoline.

Other reactions which may amount to attack by nucleophiles on the quinoline molecule [22] also support the order 2 < 4 < others for the π-electron densities. However, it is possible that these reactions, and also the amination discussed above, involve initial addition of an electrophile [*e.g.*, Ba^{++} in amination with $Ba(NH_2)_2$] to the nitrogen lone-pair of electrons, followed by nucleophilic attack on the quinolinium system thus formed. The catalysis by Ba^{++} observed in the amination tends to support this proposition.

Evidence for the order of π-electron densities in the quinoline molecule might alternatively be sought in the relative reactivities of methyl substituents towards aldehydes and other reagents. Electrophilic catalysts such as anhydrous zinc chloride are commonly employed, and this again leads to ambiguity as to the nature of the reactive species since the catalyst may attach itself to the nitrogen *n*-electrons, thus producing a quinolinium structure (nitrogen core charge +2).* However, in some cases,[23] a basic catalyst or no catalyst has been used. The greater reactivity of a 2- than of a 4-methyl substituent in quinoline under these conditions implies that the π-electron densities increase in the order 2 < 4 < others in the free base.†

Several reactions which undoubtedly involve nucleophilic attack on the quinolinium system have been observed when using 1-alkylquinolinium salts and related compounds. They show an interesting variation in the orientation of attack which has been studied particularly by Bradley and Jeffrey.[24] With strong nucleophiles such as R^- or OH^- the attack occurs at the 2-position, while with the weaker nucleophile CN^- the 4-position is attacked. Now vigorous reagents will demand less π-electron rearrangement in formation of the transition state than will weak reagents,[20] so that it might be suspected that the orientation of attack by strong nucleophiles will tend to follow the π-electron distribution whereas with weaker nucleophiles the atom-localization energies will be decisive. The change in orientation can be accounted for in this way. The π-electron densities for the quinolinium system are shown in Fig. 5. For $h' < 0{\cdot}22$ the 2-position has the lowest charge, whereas for $h' > 0{\cdot}09$ the 4-position has the smallest localization energy (Fig. 6), so that for h' in the range 0·09—0·22 the change in orientation can be explained.‡

Some quantitative studies of the ease of displacement of halogen substituents in quinoline by nucleophiles have been made,[25] the activation energies being in the order 2 < 4 < others with a weak nucleophile (piperidine), and 4 < 2 with a strong nucleophile (ethoxide anion). The theoretical interpretation is complicated by the fact that the halogen substituents conjugate with the ring system, which introduces additional coulomb and resonance parameters into any Hückel molecular-orbital calculations. We have, therefore, not attempted detailed calculations for such systems. It is tempting to connect the change in relative reactivities of substituents with strength of nucleophile with the proposition that the π-electron density at the attacked position is decisive for strong nucleophiles, the localization energy at that position in the case of weak nucleophiles. However, at present there is no clear evidence that the relative reactivities of two positions

* The alternative rôle of the catalyst commonly assumed in these reactions is attachment to the *n*-electrons of the aldehydic oxygen atom, but both modes of attachment could operate in the heterocyclic reactions.

† If the reaction mechanism consisted of an ionization pre-equilibrium followed by reaction of the aldehyde with the small equilibrium amount of conjugate base formed in the first step, then the relative reactivities of the various methylquinolines would be determined largely by the relative stabilities of their conjugate bases. It is not possible to account for the observed order of reactivities in this way because the conjugate base of 4-methylquinoline is more stable than that of 2-methylquinoline; the difference in π-electron energies (for $h = 0{\cdot}5$, $h' = 0{\cdot}085$) is $0{\cdot}045\beta^0$.

‡ The lower limit depends somewhat on the value adopted for β^0_{CN}, the figure given here applying for $\beta^0_{CN} = \beta^0$. For $\beta^0_{CN} = 1{\cdot}2\beta^0$, however (see Fig. 7), any positive value of h' yields the appropriate order of nucleophilic localization energies.

[22] Bergstrom and McAllister, *J. Amer. Chem. Soc.*, 1930, **52**, 2845; Bergmann and Rosenthal, *J. prakt. Chem.*, 1932, **135**, 267.

[23] Kaslow and Stayner, *J. Amer. Chem. Soc.*, 1945, **67**, 1716.

[24] Bradley and Jeffrey, *J.*, 1954, 2770.

[25] Brower, Samuels, Way, and Amstutz, *J. Org. Chem.*, 1953, **18**, 1648; Chapman and Russell-Hill, *Chem. and Ind.*, 1954, 1298.

in two *different* conjugated systems are solely determined by the relative π-electron densities at these positions (clearly no such simple relation holds for positions in different alternant hydrocarbons) and it does not seem profitable to consider further these substituted quinolines at present.

Attack by Electrophiles.—The orientation of electrophilic substitution in quinoline and its derivatives is often regarded as puzzling [26] because the position preferentially nitrated, for example, can be 3, 5, 6, or 8. It now seems possible to account for all of the observations in terms of molecular-orbital calculations. The key observations concern the parent heterocycle: in a strongly acidic environment quinoline is nitrated,[7,27] brominated,[9,10] and sulphonated [28] at the 8- and the 5-position, whereas in a less acidic environment the order of reactivity of positions in nitration,[8] bromination,[9] and mercuration [29] is 3 > 6,8. It was suggested [5] that in the strongly acidic medium (concentrated sulphuric acid) the

FIG. 9. *Electrophilic localization energies of quinolinium* ($h = 2$, $\beta^0_{CN} = \beta^0$) *as a function of the auxiliary inductive parameter.*

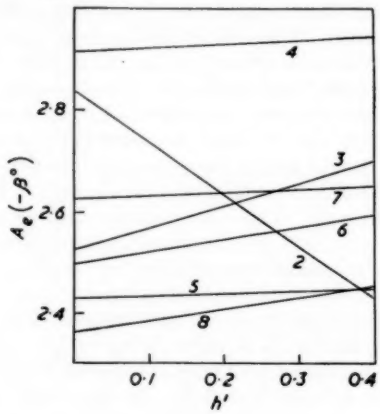
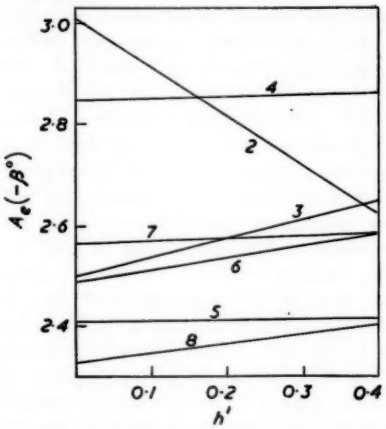


FIG. 10. *Electrophilic localization energies of quinolinium* ($h = 2$, $\beta^0_{CN} = 1{\cdot}2\beta^0$) *as a function of the auxiliary inductive parameter.*



unprotonated quinoline is present in too small a concentration to react appreciably with the electrophile, the reaction proceeding through the quinolinium cation. The latter must be relatively unreactive towards cations because it is a cation too. Thus the orientation of electrophilic substitution is likely to follow atom-localization energies rather than π-electron densities, as discussed above for nucleophilic substitution. The localization energies for electrophilic substitution are shown in Figs. 8, 9, and 10 and they are smallest for the 8- and the 5-position.

It was also suggested [5] that in acetic anhydride or acetic acid the proportion of unprotonated quinoline is great enough for electrophilic substitution to proceed predominantly through it, the free base being reactive enough for the orientation to be governed by the π-electron densities. The π-electron densities of quinoline are greatest for the 3-, 6-, and 8-positions and although the values available in the literature [2,6] when the suggestion was made did not fall in the order 3 > 6,8 > others, it was thought that this order might be obtained with a more appropriate choice of Hückel parameters. However, the present study (Figs. 1 and 2) shows that for no physically reasonable choice of parameters does the 3-position have the greatest π-electron density.

[26] Campbell, "Chemistry of Carbon Compounds," Elsevier, Amsterdam, 1957, Vol. IVA, p. 597; Elderfield, "Heterocyclic Compounds," Wiley, New York, 1952, Vol. IV, p. 262.
[27] Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1940, **62**, 1640.
[28] McCasland, *J. Org. Chem.*, 1946, **11**, 277.
[29] Ukai, *J. Pharm. Soc. Japan*, 1931, **51**, 542.

Dewar and Maitlis [8] proposed a different explanation to account for the orientation 3 > 6,8 > others, involving the initial 1,2-addition of nitronium acetate and subsequent substitution in the dihydroquinoline system. Since this system does not carry a positive charge the orientation of electrophilic substitution would be expected to follow π-electron densities. These are shown in Fig. 11 (the nitrogen core charge in the dihydroquinoline system is +2, so that the parameters for quinolinium are appropriate). However, the order of π-electron densities does not coincide with the observed orientation of nitration for any acceptable value of h'.

An alternative mechanism which does account for the observed orientation of nitration, bromination, and mercuration is suggested from the preceding discussion of nucleophilic attack in quinolinium systems. If the nucleophile is as weak as or weaker than CN^-—and the acetate anion is in this category, as judged by its basicity—it attacks the 4-position. The π-electron densities for the resultant 1,4-dihydroquinoline system are shown in Fig. 12.

FIG. 11. *π-Electron densities for* 1,2-*dihydroquinoline* ($h = 2$) *as a function of the auxiliary inductive parameter.*

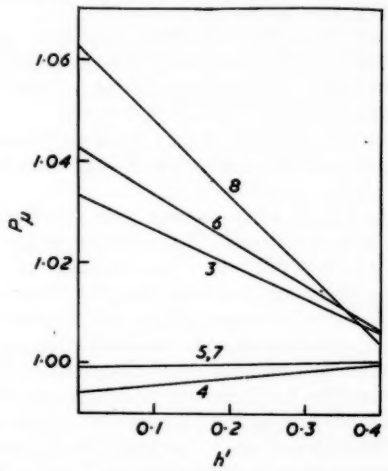
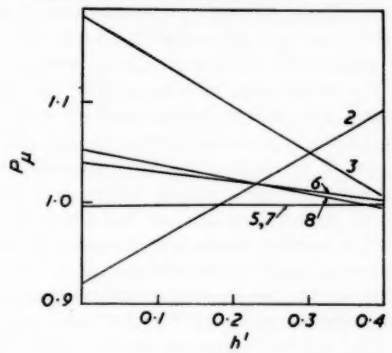
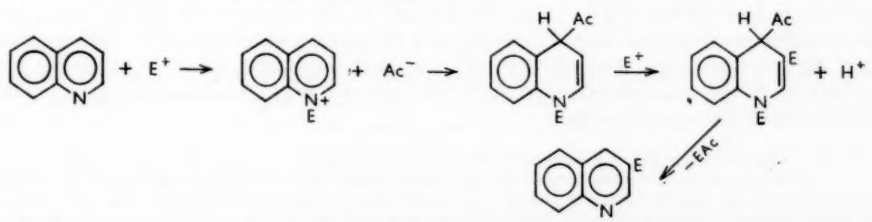


FIG. 12. *π-Electron densities for* 1,4-*dihydroquinoline* ($h = 2$) *as a function of the auxiliary inductive parameter.*



For $h' < 0{\cdot}30$ the 3-position has the greatest π-electron density. We therefore suggest that the preferential attack of the 3-position in bromination or nitration in acetic acid or anhydride occurs by initial " electrophilation " of the nitrogen followed by addition of acetate at the 4-position of this quinolinium system, then by electrophilic substitution in the 1,4-dihdroquinoline system, and finally by elimination of " electrophile acetate: "



The smaller amount of attack at the 6- and the 8-position might be accounted for in a similar way, since these positions are next in order of π-electron densities in 1,4-dihydroquinoline. However, the observation [8] that not even a trace of 3-nitroquinoline could be isolated when nitration was performed in perfluoroacetic anhydride, the products being

the 6- and the 8-nitro-derivative, suggests that these isomers are formed by direct electrophilic substitution in the quinoline molecule, trifluoroacetate anion being too weak a nucleophile to form the 1,4-dihydroquinoline system. The 6- and the 8-substituted product in acetic acid or anhydride may thus be formed by attack on the small proportion of "unelectrophilated" quinoline present in these solvents. If this mechanism operates, then the order of reactivities is expected to be (see Fig. 2) $8 > 6$ (for the physically likely range of $0{\cdot}07 < h' < 0{\cdot}16$).* Unfortunately the experimental evidence at present available does not indicate unambiguously the relative reactivites of these two positions. Dewar and Maitlis did not separate the 6- and the 8-nitroquinoline and, although the only major bromination products in acetic acid are [9] 3-, 3,6-, and 3,6,8-substituted quinolines, this does not necessarily imply that the 6-position is more reactive than the 8-position because the trisubstituted product predominates even when only one mol. of brominating agent is used and this product might largely or wholly be formed by way of the 3,8- rather than the 3,6-dibromo-compound. The preponderance of polysubstituted products does, however, support the hypothesis that the second and third substitutions occur in the free base because the explanation of polysubstitution must be sought [5] in the considerable lowering of the basicity of quinoline produced by bromo-substituents.

Mercuration with mercuric acetate in methanol [29] which leads ultimately to 3- and 8-substituted products proceeds through isolable intermediates which may be 1,4-adducts of the type here proposed to account for 3-orientation. Again the available evidence is not sufficiently clear-cut to decide whether the order of reactivities is $8 > 6$ or not.

The orientation of electrophilic substitution in isoquinoline in not too strongly acidic media [9] also can be interpreted by using molecular-orbital calculations [30] and assuming an addition mechanism similar to that described above.

Attack by Radicals.—The phenylation of quinoline with benzoyl peroxide [31] undoubtedly involves attack of the free base by phenyl radicals. The relative yields of phenyl derivatives are in the order $8 > 4 > 3 > 5 > 6,7 > 2$. The isolation of all possible isomers shows that phenyl radicals are not very selective and thus that they are extremely reactive towards quinoline. It might therefore be expected that the orientation would follow the molecular-orbital quantities corresponding to the "isolated molecule" treatment of reactivity [32] rather than radical localization energies. For alternant hydrocarbons the free valencies are the appropriate quantities but these are no longer apposite for non-alternant or heterocyclic systems,[33] and no alternative satisfactory "isolated molecule" quantities have so far been suggested for such systems. Certainly the observed orientations cannot be correlated with the localization energies (Fig. 13).

The high-temperature bromination of quinoline,[34] to yield 2-bromoquinoline, probably involves attack of quinoline by bromine atoms. The more severe discrimination between the quinoline positions, and the gross change in relative reactivities of positions, compared with the phenylation phenomena, suggest that if this reaction involves radical attack then the orientation should be governed by the localization energies. The localization energies for the free base, shown in Fig. 13, do not account for the observed orientation, but those for the quinolinium system (Figs. 14 and 15) do if β^0_{CN} is not greater than β^0.† This suggests that the reaction may proceed through a quinoline–bromine complex involving the n-electrons of the quinoline-nitrogen atom, the complex thus resembling the quinolinium system rather than quinoline itself.

* In 1,4-dihydroquinoline the order is $8 > 6$ for $h' < 0{\cdot}25$ and $6 > 8$ for $0{\cdot}25 < h' < 0{\cdot}38$.

† For the quinolinium system a value of β^0_{CN} less than that for quinoline would indeed be appropriate because the effective nuclear charge on the quinolinium-nitrogen is greater than that on the quinoline-nitrogen atom, and β^0_{CN} decreases with increasing nuclear charge of either carbon or nitrogen.

[30] Brown and Harcourt, *Tetrahedron*, in the press.
[31] Pausacker, *Austral. J. Chem.*, 1958, **11**, 200.
[32] Brown, *Quart. Rev.*, 1952, **6**, 63.
[33] Brown, *J. Chim. phys.*, 1953, **50**, 109.
[34] Jansen and Wibaut, *Rec. Trav. chim.*, 1937, **56**, 699.

The change in the orientation of vapour-phase bromination of quinoline at low temperatures, when 3-bromoquinoline is produced,[34] cannot be reconciled with the localization energies. However, a homolytic mechanism analogous to the heterolytic mechanism proposed to account for electrophilic substitution at the 3-position may be tentatively proposed. It is possible that at lower temperatures a complex between quinoline and

FIG. 13. *Radical localization energies for quinoline ($h = 0.5$) as a function of the auxiliary inductive parameter.*

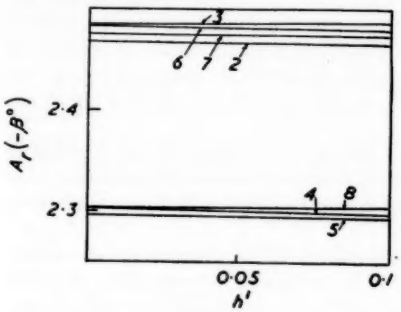
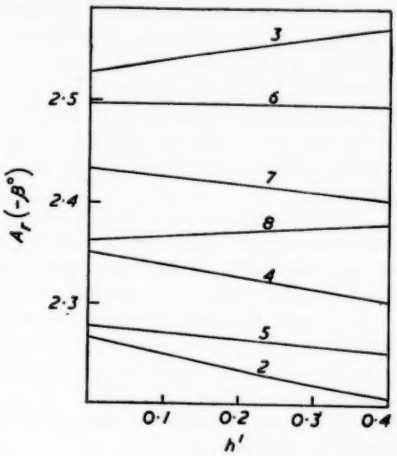


FIG. 14. *Radical localization energies of quinolinium ($h = 2$, $\beta^0_{CN} = \beta^0$) as a function of the auxiliary inductive parameter.*



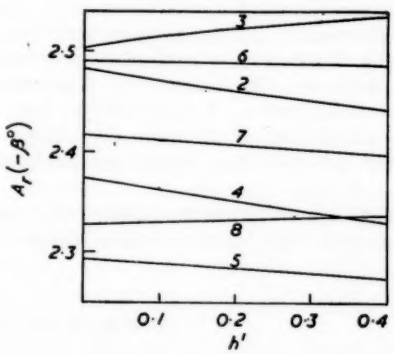


FIG. 15. *Radical localization energies of quinolinium ($h = 2$, $\beta^0_{CN} = 1{\cdot}2\beta^0$) a function of the auxiliary inductive parameter.*

bromine (somewhat similar in type to that suggested to account for the features of electrophilic substitution [35] but with the bromine engaging both the 1- and the 2-position of quinoline) is formed in sufficient concentration for the bromination to proceed by homolytic attack by bromine on this 1,2-dihydroquinoline system. The attack would occur at the 3-position because this is now equivalent to the ω-styrene position.*

Conclusion.—In the above analysis it has been shown that it is possible to account,

* The distinction between a 1,2-complex and a 1,2-adduct is that in the former the Br–Br bond remains intact and the nitrogen atom of quinoline is excluded from the conjugation. In the latter the Br–Br bond is broken and the nitrogen still participates in the conjugation but with a core charge of +2.

[35] Brown, *J.*, 1959, 2224, 2232.

sometimes very speculatively, for many substitutions in quinoline by using simple Hückel molecular-orbital calculations as a basis, with values of parameters close to those indicated by other studies. The analysis suggests that the following is a suitable set of Hückel parameters: $\beta^0_{CN} = \beta^0$; for N (core charge +1), $h = 0{\cdot}5$, $h' = 0{\cdot}085$; for NH (core charge +2), $h = 2$, $h' = 0{\cdot}2$.

In addition, the study provides further evidence for the principle that when reactions occur readily the orientation tends to follow the charge distribution (for heterolytic reactions), while for more sluggish reactions the orientation tends to follow the localization energies. These values may be compared with previous estimates of coulomb parameters based on comparison of theoretical and experimental data. One method of estimation uses the basicity constants of heterocylic amines.[36-8] The results reported have been $h_{NH} - h_N \approx 1{\cdot}2$,[36] $h_N \approx 0{\cdot}6_5$,[37] $h_{NH} = 2$, $h_N = 0{\cdot}8$;[38] but although these values are reasonably close to those found in the present study there are considerable uncertainties in the method; the variance in the linear correlations used is considerable, a conversion factor, for which widely varying estimates have been proposed, is required to convert from kcal. mole^{-1} into Hückel units (*i.e.*, units of β^0), and the auxiliary inductive effect was neglected.

Another estimate, $h_N = 0{\cdot}6$,[39] has been based on the dipole moments of six-membered-ring heterocycles. This also is now regarded as unsatisfactory because the estimate used for the σ-electron contribution to the dipole moment is now considered to be unsatisfactory and no auxiliary inductive parameter was included.

The value $h_N = 0{\cdot}5$ has been derived from consideration of the proportions of isomers isolated in the phenylation of pyridine.[40] This too is unreliable because (i) it depends upon the assumption that the orientation should be correlated quantitatively with localization energies rather than some " isolated molecule " quantities, (ii) there is some doubt as to the interpretation of phenylation experiments,[31] and (iii) no auxiliary inductive parameter was included.

It must be emphasized that the present study does not furnish a sensitive means of fixing the values for the primary coulomb parameters h_N and h_{NH} because agreement with experiment can be obtained over an appreciable range of these parameters provided that values for the auxiliary inductive parameters are chosen appropriately. The present work primarily demonstrates that, given the values of h_{NH} and h_N, it is possible to account for the chemistry of quinoline for values of h'_{HN} and h'_N which are physically reasonable, lie within narrowly defined numerical ranges, and have also been found suitable in similar studies of other nitrogen heterocycles.

The present investigation strongly suggests that a variety of mechanisms may operate in substitution of quinoline and that these reactions might prove a fertile field for future studies.

UNIVERSITY OF MELBOURNE, CARLTON, N.3,
VICTORIA, AUSTRALIA.

[*Received, March 2nd*, 1959.]

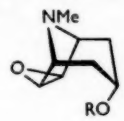
[36] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 275.
[37] Hush, *J.*, 1953, 684.
[38] Mason, *J.*, 1958, 674.
[39] Lowdin, *J. Chem. Phys.*, 1951, **19**, 1323.
[40] Brown, *J.*, 1956, 272.

698. *The Stereochemistry of the Tropane Alkaloids. Part XII.* The Total Synthesis of Scopolamine.*

By P. Dobó, G. Fodor, G. Janzsó, I. Koczor, J. Tóth, and I. Vincze.

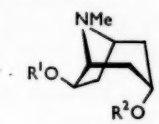
A stereospecific synthesis of scopolamine has been achieved, starting from tropane-3α,6β-diol, which was converted into 3α-acetoxytrop-6-ene, and thence into *O*-acetylscopine (3α-acetoxy-6β,7β-epoxytropane). Hydrolysis, followed by acylation with *O*-acetyltropoyl chloride and hydrolysis, gave (±)-scopolamine, the resolution of which has been described earlier. The biogenesis of hyoscyamine and scopolamine is discussed.

Earlier work has indicated [1] that (−)-hyoscine,[2] an alkaloid of *Hyoscyamus muticus* and *H. niger*, is an optically active form of (±)-scopolamine, an alkaloid [3] of *Scopolia atropoides*, the bases being respectively optically active and racemic forms of 6,7-epoxy-3-tropoyloxytropane (I; R = CO·CHPh·CH_2·OH).[1] The alkamine common to the two alkaloids was obtained later,[4] but could not be reconverted into scopolamine. The respective β- and α-orientations of the epoxide bridge and the acyloxy-group in the alkaloids have been proved by stereochemical considerations [5] of the conversion [4] of scopine into oscine, and by hydrogenolysis [6] of scopolamine into (−)-tropane-3α,6β-diol.[7]



(I)

(II)



(III)

Robinson-type tropinone syntheses using epoxysuccindialdehyde [8] and maleic dialdehyde [9] as the aldehyde components are attended by difficulties. It seemed to us that a valuable intermediate in the synthesis of scopolamine would be trop-6-en-3α-ol (II; R = H), a suggested common intermediate for the biogenesis of several tropane alkamines.[10] This compound should be obtainable by selective dehydration of tropane-3α,6β-diol (III; $R^1 = R^2 = H$), available synthetically,[11] and should be epoxidisable to (I; R = H).

We have now effected the total synthesis of scopolamine by a route involving these intermediates.[12] 3α-Acetoxytrop-6-ene (II; R = Ac) has been obtained by two procedures.[12a] In the first of these 6β-phenylcarbamoyloxytropan-3α-ol (III; R^1 = Ph·NH·CO, R^2 = H), obtained [13] from 6β-phenylcarbamoyloxytropinone, gave, on treatment with acetyl chloride, 3α-acetoxy-6β-phenylcarbamoyloxytropane (III; R^1 = Ph·NH·CO, R^2 = Ac), which on distillation *in vacuo* afforded 3α-acetoxytropan-6β-ol

* Part X, Fodor, Tóth, and Vincze, *J.*, 1957, 1349; Part XI, Halmos, Kovács, and Fodor, *J. Org. Chem.*, 1957, **22**, 1699.

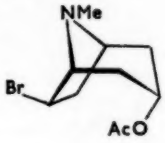
[1] For a detailed review see H. L. Holmes, in Manske and Holmes, "The Alkaloids," Academic Press, Inc., New York, 1950, Vol. I, pp. 302—305.
[2] Ladenburg, *Annalen*, 1881, **206**, 274.
[3] Schmidt, *Arch. Pharm.*, 1892, **230**, 207.
[4] Willstätter and Berner, *Ber.*, 1923, **56**, 1079.
[5] Fodor, *Nature*, 1952, **170**, 278; Meinwald, *J.*, 1953, 712; Cookson, *Chem. and Ind.*, 1953, 337.
[6] Fodor, Kovács, and Meszáros, *Research*, 1952, **5**, 534; Fodor and Kovács, *J.*, 1953, 2341.
[7] For the configuration of tropane-3α,6β-diol see Mitchell and Trautner, *J.*, 1947, 1330; Fodor, Tóth, and Vincze, *Helv. Chim. Acta*, 1954, **37**, 907.
[8] Schöpf and Schmetterling, *Angew. Chem.*, 1952, **64**, 591.
[9] Preobrashenski, Rubtsov, Dankova, and Pavlov, *J. Gen. Chem.* (*U.S.S.R.*), 1945, **25**, 952.
[10] Cromwell, *Biochem. J.*, 1943, **37**, 707, 722, and previous publications.
[11] Stoll, Becker, and Jucker, *Helv. Chim. Acta*, 1952, **35**, 1263; Stoll, Lindenmann, and Jucker, *ibid.*, 1953, **36**, 1526.
[12] Cf. preliminary reports: (*a*) Fodor, Tóth, Koczor, and Vincze, *Chem. and Ind.*, 1955, 1260; (*b*) Fodor, Tóth, Koczor, Dobó, and Vincze, *ibid.*, 1956, 754.
[13] Vincze, Tóth, and Fodor, *J.*, 1957, 1349.

(III; $R^1 = H$, $R^2 = Ac$). The same monoester was also obtained by selective Kunz hydrolysis of 3α,6β-diacetoxytropane (III; $R^1 = R^2 = Ac$), and its toluene-*p*-sulphonate ester when heated with collidine yielded 3α-acetoxytrop-6-ene (II; R = Ac).

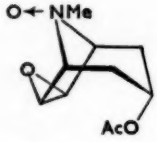
The second route involved dehydration of (±)-tropane-3α,6β-diol (III; $R^1 = R^2 = H$) with phosphoryl chloride to (±)-3α,6α-epoxytropane (IV),[14] by an S_N2i mechanism.[15] Acetobromolysis of the oxide (IV) afforded 3α-acetoxy-6β-bromotropane (V); dehydrobromination then yielded the acetate (II; R = Ac). The constitution of the last was proved by hydrogenation to 3α-acetoxytropane;[12a] this provides a direct correlation of the 3-hydroxyl groups of scopolamine and valeroidine with tropine. Alkaline or acid hydrolysis of 3α-acetoxytrop-6-ene gave trop-6-en-3α-ol (II; R = H).

Treatment of the acetate (II; R = Ac) with monoperphthalic acid afforded the *N*-oxide as the major product;[12a] an excess of the per-acid gave a poor yield of *O*-acetylscopine *N*-oxide (VI).[12b] The latter on hydrogenation yielded 3α-acetoxytropan-6β-ol (III; $R^1 = H$, $R^2 = Ac$), indicating *exo*-formation of the epoxide ring. Under acidic conditions no epoxidation occurred, owing to deactivation of the ethylenic bond by the positively charged tropanium nitrogen atom.[15]

(IV)



(V)



(VI)

The required epoxidation was finally effected by using trifluoroperacetic acid[16] which, with 3α-acetoxytrop-6-ene trifluoroacetate in methylenechloride–acetonitrile, gave *O*-acetylscopine (I; R = Ac), identified as the picrate.[17] A better yield was obtained by epoxidation with formic acid and 80% hydrogen peroxide. The epoxide and unchanged olefin were separated by paper chromatography in butanol–N-hydrochloric acid. An authentic specimen of *O*-acetylscopine was prepared[12b] from scopine[4] (I; R = H) by treatment of its hydrochloride with acetyl chloride.

The synthesis was completed by a Kunz[18] hydrolysis of *O*-acetylscopine to scopine (small amounts of oscine were formed simultaneously[12b]). Acylation of the carbinol base with (±)-*O*-acetyltropoyl chloride proved to be difficult. When the free base was used, only *O*-acetyloscine[19] was obtained, identified as its picrate. The observation that (−)-*O*-acetyltropoyl chloride was easily racemised by bases, possibly because of the formation of a keten as an intermediate product, prompted us to attempt the acylation of scopine hydrochloride. However, heating the salt with (±)-*O*-acetyltropoyl chloride[20] in chloroform solution gave no *O*-acetylscopolamine; paper chromatography showed the presence of some *O*-acetylscopine and a more mobile compound.* Eventually it was found that in nitrobenzene at 65° scopine hydrochloride and an excess of the acid chloride gave *O*-acetylscopolamine[21] (I; R = CO·CHPh·CH_2·OAc), accompanied by the same unidentified compound. The product was separated by partition chromatography on cellulose, with elution with butanol–N-hydrochloric acid, and then hydrolysed by acid to

* A detailed paper-chromatographic study of this and other acylation experiments is being carried out by Dr. O. Kovács.

[14] (−)-Tropene oxide has been described by Wolfes and Hromatka, *Merck's Jahresber.*, 1934, **47**, 45.
[15] Fodor, Lecture, Leipzig, October 23, 1955; *Angew. Chem.*, 1956, **68**, 153; *Tagungsber. Chem. Ges. DDR.*, 1955, 105.
[16] Emmons, *J. Amer. Chem. Soc.*, 1954, **76**, 348; Emmons and Pagano, *ibid.*, 1955, **77**, 89.
[17] Fodor, Lecture, Univ. Münster, November 3, 1955; *Angew. Chem.*, 1956, **68**, 188.
[18] Kunz and Hudson, *J. Amer. Chem. Soc.*, 1926, **48**, 1982.
[19] Schmidt, *Arch. Pharm.*, 1905, **243**, 559.
[20] Wolffenstein and Mamlock, *Ber.*, 1908, **41**, 723.
[21] Hesse, *J. pr. Chem.*, 1901, **64**, 353.

(±)-scopolamine (I; R = CO·CHPh·CH_2·OH), further purified by the same technique. The picrate [22] and tetraphenylborate of the synthetic product proved to be identical with the same derivatives of (±)-scopolamine.

Since (±)-scopolamine has been resolved into (+)- and (−)-hyoscine,[23 24] this synthesis is also a total synthesis of hyoscine.

Future work will be concerned with attempts to expoxidise 3α-tropoyloxytrop-6-ene (II; R = CO·CHPh·CH_2·OH) directly to scopolamine,[25] and with investigations concerning the rôle of 3-acyloxytrop-6-enes in biosynthesis. The ability of young *Datura ferox* plants to oxidise hyoscyamine to hyoscine [26] prompts us to study the effect of administering 3-acyloxytrop-6-enes to the plants.

Experimental

M. p.s are corrected.

3α-Acetoxy-6β-phenylcarbamoyloxytropane (III; R^1 = Ph·NH·CO, R^2 = Ac).—Acetyl chloride (85 ml.) was added to a suspension of 6β-phenylcarbamoyloxytropan-3α-ol (III; R^1 = Ph·NH·CO, R^2 = H) (276 g.) in dry chloroform (450 ml.) with cooling. After 4 hr. at 80° the crystalline *hydrochloride* was collected at the pump and washed thoroughly with acetone–ether (1 : 1). The yield was 312·5 g., and the m. p. 251—252° (decomp.). Evaporation of the filtrate afforded a second crop (20 g.; total yield 94%) (Found: C, 57·1; H, 6·1; N, 7·8; Cl, 9·8, 9·9. $C_{17}H_{23}O_4N_2Cl$ requires C, 57·5; H, 6·5; N, 7·9; Cl, 10·0%).

The salt was dissolved in water (1·4 l.), basified with potassium hydroxide (140 g.), and extracted with chloroform (5 × 250 ml.). The combined extracts were dried (Na_2SO_4) and evaporated, giving the free base (295 g.) as an oil.

3α-Acetoxytropan-6β-ol (III; R^1 = H, R^2 = Ac).—(*a*) The foregoing phenylurethane (295 g.) was pyrolysed at 205—250°/1—2 mm., decomposition being complete after ten such treatments. The oil so obtained (118·53 g.) was triturated with acetone, whereby crystallisation was induced. Recrystallisation from acetone gave colourless needles of *3α-acetoxytropan-6β-ol* (107·75 g., 63%), m. p. 117° (Found: C, 60·6; H, 9·0; N, 6·8. $C_{10}H_{17}O_3N$ requires C, 60·3; H, 8·6; N, 7·0%).

(*b*) 3α,6β-Diacetoxytropane (III; R^1 = R^2 = Ac) (24 g.) in acetone (700 ml.) was treated with 0·1N-sodium hydroxide (1·7 l.) and kept at 30° for 65 min. The solution was neutralised with N-hydrochloric acid (120 ml.) and, after evaporation of the acetone, adjusted to pH 10 with aqueous potassium hydroxide. Chloroform-extraction (total volume 650 ml.) gave, after evaporation, a partially crystalline mass. The crystals of the monoacetate (24 g.) were collected and washed with ether (yield 15·6 g., 78%; m. p. 117°).

3α-Acetoxy-6β-toluene-p-sulphonyloxytropane (III; R^1 = *p*-MeC_6H_4·SO_2, R^2 = Ac).—3α-Acetoxytropan-6β-ol (107·7 g.) and toluene-*p*-sulphonyl chloride (51·2 g.) were dissolved in chloroform (100 ml.) and kept at 100° for 3 hr. The solution was then diluted with chloroform (200 ml.) and shaken with water (5 × 50 ml.), and the combined aqueous layers were extracted with chloroform (50 ml.). The dried (Na_2SO_4) chloroform extracts were evaporated and the residue was triturated with ether. The crystals were collected (81 g., 84%); recrystallisation from acetone–ether gave plates, m. p. 80° (Found: N, 4·3. $C_{17}H_{23}O_5NS$ requires N, 4·0%). Basification of the aqueous layers with potassium hydroxide (50 g.), followed by chloroform extraction (5 × 50 ml.), gave unchanged 3α-acetoxytropan-6β-ol (47 g.), m. p. 116°. The *picrate* of the toluene-*p*-sulphonic ester crystallised from absolute ethanol and had m. p. 223—224° (Found: N, 9·8; S, 5·2, 5·3. $C_{23}H_{26}O_{12}N_4S$ requires N, 9·6; S, 5·5%).

3α-Acetoxytrop-6-ene (II; R = Ac).—A few drops of dimethylaniline were added to a suspension of the above toluene-*p*-sulphonic ester (35·3 g.) in collidine (162 ml.), and the mixture was heated at 190° for 2 hr. in a sealed tube. Evaporation at 55°/1 mm. gave an oil which was taken up in chloroform (150 ml.) and extracted with 10% potassium carbonate solution (250 ml.) several times, then with water (50 ml.). The chloroform solution was decolorised with charcoal, dried (Na_2SO_4), and evaporated, leaving *3α-acetoxytrop-6-ene*, b. p. 57—63°/1 mm. (12·1 g.) (Found: C, 66·4; H, 8·7; N, 7·8. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3; N,

[22] Carr and Reynolds, *J.*, 1912, **101**, 946.
[23] King, *J.*, 1919, **115**, 476.
[24] Schukina, Okun, Yurigin, and Preobrashenski, *J. Gen. Chem.* (*U.S.S.R.*), 1940, **10**, 803.
[25] Fodor, Romeike, *et al.*, Lecture, XVIth Internat. Congress Pure Appl. Chem., Paris, July 19th, 1957; *Angew. Chem.*, 1957, **69**, 678.
[26] Romeike, *ibid.*, 1956, **68**, 124.

XUM

7·7%). On catalytic hydrogenation 0·98 mol. of hydrogen was absorbed, with the formation of 3α-acetoxytropane (tropanyl acetate) [picrate, m. p. and mixed m. p. 222° (decomp.) (Found: C, 46·5; H, 4·45; N, 13·7. Calc. for $C_{16}H_{20}O_9N_4$: C, 46·8; H, 4·4; N, 13·65%)]. The *picrate* of the tropene crystallised from ethanol in needles, m. p. 210—212° (Found: N, 13·7. $C_{16}H_{18}O_9N_4$ requires N, 13·7%).

3α,6α-*Epoxytropane* (IV).—(±)-Tropane-3α,6β-diol (25 g.) was mixed with phosphoryl chloride (250 ml.) at room temperature. After 1 hr. the solution was heated at 100° for a further hour, and the excess of phosphoryl chloride removed *in vacuo*. The residue was poured on crushed ice (250 g.), and the solution decolorised (charcoal), filtered, basified to pH 9 with 10N-sodium hydroxide, and saturated with potassium carbonate. The liberated oil was isolated with ether (total volume 300 ml.), and the extracts were dried and evaporated. The residual 3α,6α-epoxytropane distilled at 50°/1 mm. (15·6 g.), as a colourless oil. The *hydrobromide* was obtained from the base (24 g.) in dry benzene (200 ml.), by treatment with acetyl bromide (13 ml.) in benzene (50 ml.). The crystalline bromide so formed was collected, washed with benzene (10 ml.), and dissolved in ethanol (200 ml.). The solution was refluxed for 20 min., decolorised (charcoal), and treated with warm ether (200 ml.). The hydrobromide, which separated as prisms (30·15 g.), m. p. 280°, was collected (Found: Br, 36·6. $C_8H_{14}ONBr$ requires Br, 36·3%).

3α-*Acetoxy*-6β-*bromotropane* (V).—The above hydrobromide (15 g.) and acetyl bromide (60 ml.) were heated in a sealed tube at 110—120° for 4 hr. Excess of acetyl bromide was removed *in vacuo*, and the residue (30 g.) dissolved in water (75 ml.). The solution was decolorised, filtered, and basified with potassium hydroxide (30 g.), and the liberated oil isolated by means of chloroform (4 × 40 ml.). The dried extracts on evaporation afforded the bromo-base, b. p. 110—115°/1 mm. (12 g.). The *picrate* crystallised from ethanol in yellow leaflets, m. p. 196° (decomp.) (Found: Br, 16·1. $C_{16}H_{19}O_9N_4Br$ requires Br, 16·3%).

Dehydrobromination of the base (8 g.) in collidine (100 ml.) containing a few drops of diethylaniline at 180° for 7 hr. under nitrogen gave, after separation of the collidine hydrobromide and removal of the excess collidine by fractionation *in vacuo*, an oil which was taken up in chloroform. The solution was washed with potassium carbonate solution and water, dried, and evaporated, yielding 3α-acetoxytrop-6-ene, b. p. 58—60°/1 mm. (2·3 g.). The picrate had m. p. 212°, alone or mixed with 3α-acetoxytrop-6-ene picrate obtained *via* the toluene-*p*-sulphonic ester (see above). On catalytic hydrogenation 3α-acetoxytropane (picrate, m. p. and mixed m. p. 222°) was obtained.

Trop-6-*en*-3α-*ol* (II; R = H).—(*a*) 3α-Acetoxytrop-6-ene (0·1 g.) in acetone (10 ml.) was mixed with 0·5N-sodium hydroxide (2 ml.) and kept at room temperature for 4 days. After removal of the solvent the oily residue was mixed with 5% ethanolic picric acid (5 ml.). *Trop*-6-*en*-3α-*ol picrate* (0·26 g.), which separated, was collected; it recrystallised from ethanol in needles, m. p. 278° (Found: C, 45·6; H, 4·55; N, 15·5. $C_{14}H_{16}O_8N_4$ requires C, 45·65; H, 4·4; N, 15·2%).

(*b*) 3α-Acetoxytrop-6-ene (1·0 g.) was refluxed for 6 hr. with 2N-hydrochloric acid (50 ml.). The solution was evaporated to dryness *in vacuo*; absolute ethanol was added and the evaporation repeated. The residual 3α-*acetoxytrop*-6-*ene hydrochloride* separated from ethanol in needles, m. p. 257—260° (decomp.) (Found: C, 54·7; H, 8·3; N, 7·8. $C_8H_{14}ONCl$ requires C, 54·7; H, 8·0; N, 8·0%). The picrate had m. p. 273°.

3α-*Acetoxytrop*-6-*ene* N-*Oxide*.—3α-Acetoxytrop-6-ene (0·1 g.) in anhydrous chloroform (1 ml.) and acetone (1 ml.) was cooled in ice and treated with 10% ethereal monoperphthalic acid (1·2 ml.). After 10 min. at 0° a sample contained 0·5 mol. of per-acid, estimated iodometrically. After 10 hr. the solvent was removed, the remaining glass dissolved in 50% potassium carbonate solution (1 ml.), and the solution extracted with chloroform (10 × 1 ml.). The combined dried extracts were evaporated and the residue was converted into the *picrate*, m. p. 168° (Found: C, 45·2; H, 5·0. $C_{16}H_{18}O_{10}N_4$ requires C, 45·1; H, 4·3%). Reaction for 20 days gave an oil which on catalytic hydrogenation (uptake: 2 mols.) afforded 3α-acetoxytropan-6β-ol, m. p. and mixed m. p. 117° (see above).

O-*Acetylscopine* (I; R = Ac) *from* 3α-*Acetoxytrop*-6-*ene* (II; R = Ac).—(*a*) 3α-Acetoxytrop-6-ene (0·362 g.), dissolved in acetonitrile (2·4 ml.), was treated with trifluoroacetic acid (2·28 g.) and cooled to 0°. A 12% solution of trifluoroperacetic acid (2·2 ml.) was added dropwise with shaking, and the mixture kept at 5° for 8 days Analysis of a sample withdrawn after 5 days showed that 80% of the peracid had been consumed. 5% Alcoholic picric acid

(10 ml.) was added, and the crude picrate [0·52 g.; m. p. 210° (decomp.)] collected and refluxed with 96% ethanol (70 ml.). The undissolved portion (m. p. 218°) was collected and crystallised from dry ethanol (10 ml.). It had m. p. 222°, alone or mixed with *O*-acetylscopine picrate obtained from natural scopolamine *via* scopine (Found: C, 45·4; H, 4·4; N, 13·3. Calc. for $C_{16}H_{18}O_{10}N_4$: C, 45·1; H, 4·3; N, 13·1%). From the mother-liquors of the crystallisation was obtained 3α-acetoxytrop-6-ene picrate, m. p. and mixed m. p. 211°.

(*b*) 3α-Acetoxytrop-6-ene (1·15 g.) was mixed with 100% formic acid (3·6 ml.), and 81% hydrogen peroxide (3 ml.) was added. After 48 hr. at 20° further hydrogen peroxide (1 ml.) was added and the mixture kept for a further 5 days. After evaporation at 20°/10 mm. to 2 ml. the residue was chromatographed in butan-1-ol–N-hydrochloric acid (5 : 1; 1 l.) on a column (175 cm. long) of cellulose powder (150 g.; Whatman Standard Grade), a 110-tube automatic fraction-collector being used. Fractions 51—100 contained *O*-acetylscopine hydrochloride (derived picrate m. p. 229°). Later fractions contained unchanged 3α-acetoxytrop-6-ene.

O-*Acetylscopine* (I; R = Ac) *from Scopolamine* (I; R = CO·CHPh·CH_2·OH).—Scopolamine was hydrolysed to scopine, m. p. 72°, as described by Willstätter and Berner.[4] Scopine (0·6 g.) was refluxed with acetyl chloride (6 ml.) for 5 hr. Evaporation gave O-*acetylscopine hydrochloride*, prisms, m. p. 231° (Found: C, 51·2; H, 7·7; N, 5·7; Cl, 14·8. $C_{10}H_{16}O_3NCl$ requires C, 51·4; H, 6·9; N, 6·0; Cl, 15·2%). The picrate had m. p. 222°.

Scopine from O-*Acetylscopine*.—(*a*) *O*-Acetylscopine was obtained from the hydrochloride by basification and chloroform-extraction. The base (1·025 g.) in acetone (50 ml.) was mixed with 0·5N-sodium hydroxide (10 ml.), and the solution filtered and kept at 25° for 10 days. Evaporation *in vacuo*, followed by treatment with ethanol (5 ml.) and 5% ethanolic picric acid, gave scopine picrate (0·638 g.), m. p. 225—232°. The picrate (0·6 g.), suspended in 96% ethanol (100 ml.), was shaken with Dowex No. 1 resin (15 g.) for 1 hr. The resin was removed and the filtrate evaporated at 35° to an oily base (0·368 g.), which was taken up in ether; the solution was dried (Na_2SO_4) and evaporated. The partly crystalline residue was collected and washed with ether, giving scopine, m. p. 72°.

(*b*) *O*-Acetylscopine (0·64 g.) in acetone (4 ml.) was treated with 0·1N-sodium hydroxide and kept at 25° for 18 hr. It was then exactly neutralised with 0·1N-hydrochloric acid and concentrated to 20 ml. Aqueous ammonia was added to pH 9·5 and the solution extracted with chloroform (5 × 10 ml.). Evaporation of the dried extracts gave a crystalline residue, which on recrystallisation from ether gave scopine, m. p. 74—76° (0·16 g., 32%).

Scopolamine from Scopine.—Scopine hydrochloride (1 g.) was powdered, suspended in nitrobenzene (7 ml.), and treated with *O*-acetyltropoyl chloride (6·5 ml.), the mixture being stirred at 50° for 38 hr. Unchanged scopine hydrochloride (0·32 g.) was removed by filtration, and the filtrate diluted with chloroform (10 ml.) and extracted with water (5 × 10 ml.). The aqueous solution, adjusted to pH 6, was extracted with chloroform (5 × 10 ml.), and the dried extracts were evaporated, leaving a viscous oil (1·15 g.). This was dissolved in butanol–hydrochloric acid and purified by chromatography on cellulose (60 g., in a column 2 m. long), as described above. Fifteen fractions of 10 ml. each, and the remainder of 5 ml., were collected. Fractions 16—25 contained *O*-acetylscopolamine; they were combined and evaporated at 50°/5 mm., leaving a yellowish oil (0·35 g.). A solution of this in N-hydrochloric acid (10 ml.) was kept at 30° for 9 hr., then evaporated to dryness at 20° *in vacuo*. The oily residue (0·24 g.) of scopolamine hydrochloride was purified by chromatography on cellulose as described above. Fractions 42—48 showed a strong mydriatic effect; they were combined and evaporated, and the residual salt treated with picric acid, giving crystalline scopolamine picrate, m. p. 175·5—176·5°, identical (mixed m. p.) with natural scopolamine picrate (Found: C, 52·1; H, 5·0; N, 11·1. Calc. for $C_{23}H_{24}O_{17}N_4$: C, 51·9; H, 4·5; N, 10·5%). The *tetraphenylborate* separated from acetone as a microcrystalline powder, m. p. and mixed m. p. 106° (decomp.) (Found: C, 78·6; H, 7·1. $C_{41}H_{42}O_4NB$ requires C, 79·0; H, 6·8%).

This work has been sponsored by the Hungarian Academy of Sciences. We thank Dr. Eva Fodor-Varga and her collaborators for the microanalyses, Mr. G. Szabadi for technical assistance, and Dr. A. R. Pinder for help in the preparation of the manuscript.

Laboratory for Stereochemical Research, Hungarian Academy of Sciences, Budapest, Hungary.
Department of Organic Chemistry, The University, Szeged, Hungary.

[*Received, April 16th*, 1959.]

XUM

699. *Mechanism of the Azide–Nitrite Reaction. Part III.*[1] *Reaction in* [^{18}O]*Water.*

By C. A. Bunton and G. Stedman.

The isotopic composition of the nitrous oxide evolved when nitrous acid and hydrazoic acid react in [^{18}O] water has been studied under conditions in which the kinetics and mechanism of the chemical reaction are known. The variation of the enrichment of the evolved nitrous oxide after complete reaction, with the concentration of azide, and with the acidity, shows that there is no appreciable hydrolysis of the intermediate nitrosyl azide in aqueous solution; all of it breaks down to nitrogen and nitrous oxide. The results show that there is exchange of oxygen atoms between nitrous acid and water with a rate law $v = k[H^+][HNO_2]$, where $k = 230$ sec.$^{-1}$ mole^{-1} l. at 0°. This has been confirmed by direct measurements of the rate of exchange of oxygen atoms between nitrous acid and water at 0°, oxygen-18 being used as a tracer. The results offer a partial explanation of discrepancies between the results of several previous investigations of oxygen exchange between nitrous acid and water, and of the kinetics of various reactions of nitrous acid, and suggest an exchange mechanism with direct attack of water upon the nitrous acidium ion, $H_2NO_2^+$, when the concentration of nitrite ion is low (<0·05N). At higher concentrations of nitrite ion, exchange is by formation of dinitrogen trioxide.

When initially isotopically normal nitrous acid reacts with hydrazoic acid in [^{18}O]water, the evolved nitrous oxide is enriched in oxygen-18:

$$HNO_2 + HN_3 \longrightarrow N_2O + N_2 + H_2O$$

Under suitable conditions the amount of exchange between nitrous acid and the solvent during the chemical reaction can be kept relatively small (<10% of the value for complete isotopic equilibration). If the reaction is always carried out under a given set of conditions, and suitable control experiments are run, reliable and consistent results can be obtained, and it is possible to use this reaction as a method of analysing for the oxygen-18 content of nitrous acid.[2] Our present object was to carry out the azide–nitrite reaction in [^{18}O] water, and to obtain information about the rate and mechanism of the exchange of oxygen atoms between nitrous acid and water from the observed enrichment of the evolved nitrous oxide. The method used was to allow " nitrite " to react with a large excess of azide under conditions where previous work [1] had revealed the rate equation and mechanism of the chemical reaction. By " nitrite " we mean all of the species present in solution that are collectively analysable as nitrous acid. In the present work the concentrations of " nitrite " were low, <0·05M, and the acidity was also low, $[H^+]$ <0·2M. Under these conditions molecular nitrous acid, HNO_2 and the nitrite ion, NO_2^- were the only species present in appreciable concentration. Hence

$$[\text{" nitrite "}] = [HNO_2] + [NO_2^-]$$

Either the " nitrite " or the solvent water was initially labelled with oxygen-18. When reaction was complete, the nitrous oxide formed was collected, purified, and analysed mass-spectrometrically.

There have been two previous quantitative investigations of the kinetics of oxygen exchange between nitrous acid and water. Bunton, Llewellyn, and Stedman [3] studied the exchange in the concentration range $[NO_2^-] = 0{\cdot}5$—2·0M at 0°. They found the rate

[1] (*a*) Part I, *J.*, 1959, 2943. Part II, *J.*, 1959, 2949.
[2] Anbar and Taube, *J. Amer. Chem. Soc.*, 1954, **76**, 6243.
[3] Bunton, Llewellyn, and Stedman, *Chem. Soc. Special Publ.*, 1957, No. 10, 1957, p. 113; *J.*, 1959, 568.

law to be $v = k_2[HNO_2]^2$, with $k_2 = 0{\cdot}53$ sec.$^{-1}$ mole^{-1} l. They interpreted this result as showing that oxygen exchange was by the formation and rehydration of dinitrogen trioxide:

$$2HNO_2 \rightleftharpoons N_2O_3 + H_2O \quad \ldots \ldots \ldots \ldots \quad (1)$$

Anbar and Taube [2] studied the exchange between nitrite and water in the presence of phosphate buffers, and concluded that the rate equation was $v = k[H^+][HNO_2]$. They interpreted this as a rate-determining formation and rehydration of the nitrosonium (nitrosyl) ion:

$$H_2NO_2^+ \rightleftharpoons NO^+ + H_2O \quad \ldots \ldots \ldots \ldots \quad (2)$$

It was hoped that the present study would throw some light on the cause of this difference in rate equations.

Experimental Method.—To obtain information on the oxygen exchange between water and nitrous acid from the isotopic abundance of the evolved nitrous oxide we must consider the kinetic forms of both exchange and chemical reaction.

Our present experiments were done with reagent concentrations such that the kinetic law was: $v = k'_c$[" nitrite "] (k'_c is constant for a given run, but depends upon $[H^+]$ and [azide]). It can be shown (Appendix) that if oxygen exchange has the rate law, $v = k'_E$ [" nitrite "] (k'_E constant for a given run, but dependent upon $[H^+]$), then with tracer in the solvent water

$$N^*_{N_2O}/(N_{H_2O} - N^*_{N_2O}) = \tfrac{1}{2}k'_E/k'_c$$

($N^*_{N_2O}$ is the isotopic abundance of evolved N_2O at complete reaction, N_{H_2O} is abundance of the water.)

Reaction and Exchange in Azide Buffer.—A series of reactions were carried out, with initially isotopically normal nitrite, and [^{18}O] water as solvent. There was always a large excess of azide buffer over " nitrite," and a large excess of isotopically enriched solvent water. The results are in Table 1.

TABLE 1. *Azide–nitrite reaction in* [^{18}O] *water at* 0°.

No.	$[HN_3]$ (M)	$[N_3^-]$ (M)	$10^5[H^+]$ (M)	[" nitrite "]$_0$ (mM)	$\frac{N^*_{N_2O}}{N_{H_2O} - N^*_{N_2O}}$	$\frac{10^5[N_3^-]N^*_{N_2O}}{(N_{H_2O} - N^*_{N_2O})}$ (M)	$\frac{N^*_{N_2O}}{N_{H_2O}}$
17	0·236	0·279	8·45	25·0	0·158	4·4	0·136
18	0·121	0·190	6·35	19·7	0·226	4·3	0·183
19	0·060	0·251	2·40	19·7	0·163	4·1	0·139
26	0·294	0·0377	78·0	4·4	1·38	5·2	0·665
27	0·113	0·219	5·15	11·4	0·270	5·9	0·223
28	0·191	0·360	5·30	3·5	0·131	4·7	0·115
29	0·219	0·352	6·20	3·8	0·139	4·9	0·121
30	0·225	0·344	6·55	17·9	0·177	6·1	0·152
31	0·225	0·344	6·55	17·8	0·189	6·5	0·162
32	0·181	0·371	4·9	6·6	0·148	5·5	0·129
35	0·046	0·0703	6·55	6·7	0·727	5·1	0·422
36	0·044	0·067	6·60	8·4	1·044	7·0	0·521
43	0·119	0·184	6·45	3·4	0·386	7·1	0·276
44[a]	0·022	0·046	4·55	2·6	1·170	5·4	0·540
45[b]	0·022	0·046	4·55	2·6	0·370	1·7	0·268
46[c]	0·022	0·046	4·55	2·6	0·390	1·8	0·280

[a] 0·406M-$NaClO_4$ added. [b] 0·406M-NaBr added. [c] 0·406M-NaCl added.

The ratio $N^*_{N_2O}/(N_{H_2O} - N^*_{N_2O})$ is sensibly independent of the concentrations of both nitrite and hydrogen ions, but it is dependent upon the concentration of azide ions (Figure). If exchange had the kinetic form $v \propto$ [" nitrite "]^n, $n \neq 1$, then $N^*_{N_2O}/(N_{H_2O} - N^*_{N_2O})$ would vary with the concentration of nitrite. Thus we establish that in the conditions of these experiments there is an oxygen exchange which is of the first order with respect to the concentration of " nitrite."

XUM

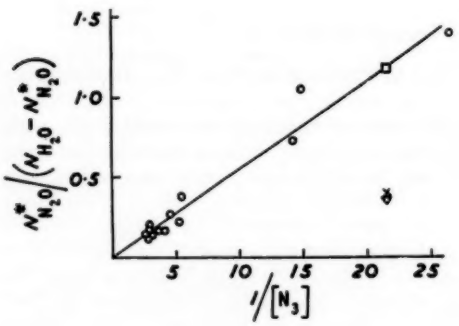
The kinetics of the azide–nitrite reaction in the presence of a large excess of azide buffer have been described in Part II. The rate equation is $v = k_3^{N_3^-}[H^+][HNO_2][N_3^-]$. There are two reasonable mechanisms for this reaction which are consistent with this rate equation. One is the formation of nitrosyl azide by a rate-determining attack of azide ions on an equilibrium concentration of nitrosonium ions, followed by a rapid breakdown of nitrosyl azide to the final products:

$$H_2NO_2^+ \underset{\text{fast}}{\rightleftharpoons} NO^+ + H_2O \xrightarrow[\text{slow}]{N_3^-} N_3NO \xrightarrow[\text{fast}]{} N_2 + N_2O$$

The other possibility is a rate-determining nucleophilic attack by the azide on the nitrous acidium ion to form nitrosyl azide, which breaks down in a subsequent fast step:

$$H_2NO_2^+ + N_3^- \xrightarrow[\text{slow}]{} H_2O + N_3NO \xrightarrow[\text{fast}]{} N_2 + N_2O$$

The first of these mechanisms would require the rate of oxygen exchange between nitrous acid and water by the formation and rehydration of the nitrosonium ion to be much more rapid than the rate of the chemical reaction to form nitrous oxide, and hence it would be



Relation between concentration of azide and the isotopic abundance of the nitrous oxide evolved.
□ $NaClO_4$, 0·406M. ▽ NaBr, 0·406M.
× NaCl, 0·406M.

expected that the evolved nitrous oxide would have the same isotopic composition as the solvent. The results in the final column of Table 1 show that the enrichment of the nitrous oxide in oxygen-18 is much less than that of the solvent water, and hence that mechanism (2) must be rejected.

Previous work [1,3,4] has shown that the rate equations for the formation of the nitrosyl compounds NOX, where X = Cl, Br, NCS, I, NO_2, and N_3 are of the form $v = k_3^{X^-}[H^+][HNO_2][X^-]$, and that the values of $k_3^{X^-}$ vary by less than a factor of three. We therefore conclude that mechanisms analogous to (2) must be rejected in all these cases; a similar conclusion has been drawn for diazotisation.[4]

The results in the seventh column of Table 1 and in the Figure show that the quantity $[N_3^-]N^*_{N_2O}/(N_{H_2O} - N^*_{N_2O})$ is approximately constant over a wide range of values of $[HN_3]$, $[N_3^-]$, $[H^+]$, and [" nitrite "]$_0$, except in the presence of added halide ion. As the rate equation for chemical reaction is $v = k_3^{N_3^-}[H^+][HNO_2][N_3^-]$ the rate equation for oxygen exchange must be $v = k[H^+][HNO_2]$. The value of $k_3^{N_3^-}$ is 2340 sec.$^{-1}$ mole^{-2} l.^{2}; from the results in Table 1, it follows that $k \doteq 260$ sec.$^{-1}$ mole^{-1} l. This value is subject to a considerable uncertainty (*ca.* ±20%).

The above results also show that there is no significant exchange by the hydrolysis of

[4] Hughes, Ingold, and Ridd, *J.*, 1958, 58, and accompanying papers.

nitrosyl azide. If we suppose that a fraction, α, of all of the nitrosyl azide molecules formed are hydrolysed back to nitrous and hydrazoic acids:

$$N_3NO + H_2{}^{18}O \longrightarrow H_2N^{18}OO^+ + N_3^- \xrightarrow[\text{fast}]{} HN^{18}OO + NH_3$$

while the remaining fraction, $1 - \alpha$, breaks down to nitrogen and nitrous oxide:

$$N_3NO \longrightarrow N_2 + N_2O$$

then it is clear that (rate of exchange)/(rate of reaction) $= k'_E/k'_c = 2N^*_{N_2O}/(N_{H_2O} - N^*_{N_2O}) = \alpha/(1 - \alpha)$, and should be independent of the azide concentration, and there would be a positive intercept at $1/[N_3^-] = 0$ in the Figure. The results show that k'_E/k'_c is proportional to $[N_3^-]^{-1}$. There is no sign of any component in the rate equation for exchange leading to a value of k'_E/k'_c independent of $[N_3^-]$, and hence there is no appreciable hydrolysis of nitrosyl azide.

Reaction in Excess of Perchloric Acid.—The above results refer to oxygen exchange at relatively low acidities (pH $\sim$ 5). At higher acidities ($[H^+] > 0{\cdot}05$M) and with suitable concentrations of nitrous and hydrazoic acids, the azide–nitrite reaction has the mechanism:

$$HN_3 + H_2NO_2^+ \xrightarrow[\text{slow}]{} H^+ + H_2O + N_3NO \xrightarrow[\text{fast}]{} N_2 + N_2O$$

The rate equation is $v = k_3^{HN_3}[H^+][HNO_2][HN_3]$. By carrying out isotopic experiments similar to those described in the previous section it is possible to make quantitative measurements of the rate of oxygen exchange between nitrous acid and water at acidities where exchange would be too fast for direct measurement. All previous measurements of oxygen exchange between nitrous acid and water have been made at low acidities (pH > 4·5).[2,3]

A slight modification of the procedure is necessary. For reaction in azide buffers, with concentration of azide ions >0·05M, the rate of the chemical reaction is markedly greater than the rate of oxygen exchange, and hence the difference between $N^*_{N_2O}$ and N_{H_2O} is large enough for accurate measurement. For reaction in excess of perchloric acid the rate of chemical reaction is much less than the rate of exchange. This is because in azide buffers the species attacking the nitrous acidium ion is the azide ion, while in excess of perchloric acid it is the much more weakly nucleophilic hydrazoic acid. As the chemical rate is much less than the exchange rate, the value of $N^*_{N_2O}$ is only slightly less than N_{H_2O}. Hence $N_{H_2O} - N^*_{N_2O}$ cannot be accurately measured. To overcome this difficulty, reaction was carried out with initially isotopically enriched sodium nitrite, in isotopically normal water (then the evolved nitrous oxide is only slightly enriched in oxygen-18). The equation relating the isotopic abundance of reactants and products can be rearranged to:

$$(N_{Nit} - N^*_{N_2O})/N^*_{N_2O} = \tfrac{1}{2}k'_E/k'_c$$

where N_{Nit} = atoms % excess of oxygen-18 in the nitrite, initially. The quantities $N^*_{N_2O}$ and $N_{Nit} - N^*_{N_2O}$ can be measured accurately (Table 2). The rate equation for chemical reaction under these conditions is $v = k_3^{HN_3}[H^+][HNO_2][HN_3]$. The sixth row of Table 2 shows that the quantity $[HN_3](N_{Nit} - N^*_{N_2O})/N^*_{N_2O}$ is approximately constant.

TABLE 2. *Isotopic experiments on the azide–nitrite reaction in excess of perchloric acid at 0°.*

No.	47	51	49	48	50
$[H^+]$ (M)	0·017	0·107	0·048	0·278	0·278
$[HN_3]$ (M)	0·175	0·035	0·175	0·175	0·175
$10^2[HNO_2]$ (M)	0·41	0·41	0·41	0·41	4·0
$10^2(N^*_{N_2O}/N_{Nit})$	4·56	1·06	4·52	5·2	5·86
$[HN_3]$ $(N_{Nit} - N^*_{N_2O})/N^*_{N_2O}$ (M)	3·7	3·3	3·7	3·5	2·8

XUM

The rate equation for exchange is therefore $v = k[H^+][HNO_2]$. If $k_3^{HN_3}$ is taken to be 34 sec.$^{-1}$ mole^{-2} l.^{2}, $k = 230$ sec.$^{-1}$ mole^{-1} l. at 0°.[2] This value is again subject to considerable uncertainty (*ca.* ±20%), but is in good agreement with the value of 260 sec.$^{-1}$ mole^{-1} l. obtained from the experiments in azide buffers. As the two sets of measurements were made in quite different regions of acidity, ($[H^+] = 0{\cdot}02$—$0{\cdot}28$M, and $[H^+] = 0{\cdot}24 \times 10^{-5}$—$7{\cdot}8 \times 10^{-5}$M) and with different mechanisms and rate equations for the azide–nitrite reaction, this " competition " method appears to be quite reliable for the determination of the rate of exchange. We consider that it should be generally applicable, and it may be of value in systems in which the rate of one of these processes is too fast for convenient measurement but the rate of the other can be determined, possibly indirectly.

The kinetic forms of the oxygen exchange do not of themselves prove that the nitrous acidium ion is formed in a pre-equilibrium proton transfer, and formulations in terms of a general acid catalysis by the proton or by molecular nitrous acid would be kinetically indistinguishable. However it is extremely difficult to formulate common mechanisms for nitrosations by nitrous acid, except by assuming that they all have the common feature of nucleophilic attack upon a preformed nitrous acidium ion (cf. refs. 1, 2, 3, 4).

We estimate $k_3^{H_2O}$, the third-order rate constant for bimolecular attack of an individual water molecule upon the nitrous acidium ion, to be 4 sec.$^{-1}$ mole^{-2} l.^{2} at 0°, *i.e.*, 1/8th that of hydrazoic acid, and *ca.* 1/150th that of the azide ion.

We can now consider the results of experiments 44, 45, and 46 (Table 1). These show that chloride and bromide ions decrease the enrichment of the evolved nitrous oxide, although perchlorate ions (in this low concentration) have no effect. Halide ions introduce a new reaction path for both exchange and chemical reaction, because nitrosyl halide (X = Br or Cl) can be formed and react with either water or azide.

$$X^- + H_2{}^{18}O{\cdot}NO^+ \xleftarrow{H_2{}^{18}O} NOX \xrightarrow{N_3^-} N_3NO + X^- \longrightarrow N_2 + N_2O$$

It appears from diazotisation experiments that nitrosyl halides are less reactive electrophiles than the nitrous acidium ion.[4] Thus they will discriminate between the abundant, but unreactive, water molecules, and the less abundant, but much more reactive, azide ions in favour of the latter, relative to the behaviour of the nitrous acidium ion. Hence the isotope abundance of the evolved nitrous oxide will be decreased by addition of halide ions.

Mechanism of Oxygen Exchange between Nitrous Acid and Water at 0°.—Previous studies [3] showed that in much more concentrated solutions of sodium nitrite (0·5—2·0M) and with concentrations of nitrous acid from 0·01 to 0·1M, the rate equation for exchange was $v \propto [HNO_2]^2$ and not $\propto [H^+][HNO_2]$. Anbar and Taube [2] concluded that there is a mechanism for oxygen exchange between nitrous acid and water with a rate equation $v \propto [H^+][HNO_2]$. However, many of their experiments were complicated by a catalysis of exchange due to the phosphate buffer that they used to control the pH, and their rate constants varied with both buffer composition and concentration. The work described in the previous sections confirms the existence of a mechanism for the exchange of oxygen atoms between nitrous acid and water, with a rate equation of the form $v \propto [H^+][HNO_2]$, and additional evidence for this exchange mechanism, also in the absence of nucleophilic buffers, has been obtained. Three experiments were carried out at 0°, with solutions of [^{18}O] sodium nitrite in isotopically normal water, acidified with perchloric acid. Exchange was stopped at suitable times by adding excess of sodium hydroxide solution. The oxygen-18 content of the nitrite was determined by allowing it to react in a sodium azide–hydrazoic acid buffer, and measuring the oxygen-18 content of the evolved nitrous oxide mass-spectrometrically. Corrections were made for the exchange occurring during reaction with the azide. These were made by using the results given in Table 1, as an empirical correction. The results are given in Table 3. The rates were obtained from two points only, and hence are subject to a considerable uncertainty. (This applies merely to the numerical values of the measured rate. The rate equation for isotopic exchange in a system in

chemical equilibrium always has a first-order form with respect to the isotopic abundances and hence no ambiguity arises in calculating the exchange rate.)

TABLE 3. *Oxygen exchange between nitrous acid and water at 0°.*

$10^3[HNO_2]$ (M)	$10^3[NO_2^-]$ (M)	10^5v (sec.$^{-1}$ mole l.$^{-1}$)	$v/[HNO_2]^2$ (sec.$^{-1}$ mole^{-1} l.)	$v/([HNO_2][H^+]$ (sec.$^{-1}$ mole^{-1} l.)
1·46	9·3	2·0	9·4	230
1·46	18·6	9·6	4·5	240
0·73	9·3	3·6	6·8	180

v is the rate of oxygen exchange between nitrous acid and water, irrespective of tracer. $[H^+]$ is calculated by taking the dissociation constant of nitrous acid [5] as $K = 3{\cdot}2 \times 10^{-4}$ mole l.$^{-1}$.

The values of $v/[HNO_2]^2$ in Table 3 are much greater than the values of k_2, the rate constant for the formation of dinitrogen trioxide. From diazotisation this is 0·85 sec.$^{-1}$ mole^{-1} l.; from oxygen exchange (with concentrations of nitrite ion >0·5M) it is 0·53 sec.$^{-1}$ mole^{-1} l. Therefore in the present experiments there is another mechanism leading to exchange between nitrous acid and water, and under these particular conditions it is much faster than the rate of formation and rehydration of dinitrogen trioxide. The results in Table 3 are consistent with a rate equation $v = k[H^+][HNO_2]$, with $k \simeq 220$ sec.$^{-1}$ mole^{-1} l., in agreement with the kinetic form of rate equation and the values of k found by the competition experiments with azide ($k \simeq 260$ sec.$^{-1}$ mole^{-1} l. in azide buffers and $k \simeq 230$ sec.$^{-1}$ mole^{-1} l. in excess of perchloric acid). This provides a direct confirmation that the interpretation of the exchange results from the azide–nitrite reaction is correct, and shows that exchange does not depend in any way upon azide.

There are two possible interpretations of the rate law $v = 230[H^+][HNO_2]$ sec.$^{-1}$ mole l.$^{-1}$ at 0°. One is that exchange occurs by the formation and rehydration of the nitrosonium ion (2). The other possibility is a bimolecular attack by the water molecule on the nitrous acidium ion:

$$H_2NO_2^+ + H_2{}^{18}O \longleftarrow H_2N^{18}OO + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The present results do not distinguish with certainty between these possibilities. The fact that amines and nucleophilic anions can be shown to substitute at the nitrous acidium ion and not at the nitrosonium ion,[1b,4] suggests that mechanism (3) is more likely than (2). Anbar and Taube [2] prefer to interpret their rate equation for oxygen exchange of $v \propto [H^+][HNO_2]$ as a rate-determining formation of the nitrosonium ion (2). They base this interpretation on a comparison of the rates of oxygen exchange and of reaction between nitrous acid and hydrogen peroxide in phosphate buffer, and on the rate of oxygen exchange between nitrous acid and water in the presence of hydrogen peroxide and phosphate buffer:

$$HNO_2 + H_2O_2 \longrightarrow HNO_3 + H_2O$$

In the presence of phosphate buffer they found that with high (4—8M) concentrations of hydrogen peroxide, the rate of the chemical reaction was independent of $[H_2O_2]$, and was of first order in $[H^+]$ and $[HNO_2]$. This rate was similar to the rate of oxygen exchange between nitrous acid and water in the absence of hydrogen peroxide. In the presence of 4M-hydrogen peroxide the rate of exchange between nitrous acid and water was much less than the value in its absence. This led them to suggest that in their experiments nitrosonium ions were captured by hydrogen peroxide as fast as they were formed:

$$H_2NO_2^+ \xrightarrow[\text{slow}]{} NO^+ + H_2O \xrightarrow[\text{fast}]{H_2O_2} HNO_3 + H_2O$$

It is difficult to interpret our experiments in the presence and in the absence of azide as reactions of the nitrosonium ion. If we assume that exchange occurs *via* NO^+ (2) then the kinetic law for the reaction in azide buffers requires that the azide ion reacts with an equilibrium concentration of nitrosonium ions, and we know this to be incorrect.

Thus we would have to assume that the azide ion reacts with predominantly the nitrous

[5] Klemenc and Hayek, *Monatsh.*, 1929, **54**, 407.

XUM

acidium ion, whereas the water reacts with NO^+ but not $H_2NO_2^+$, and it is difficult to reconcile the latter assumption with Anbar and Taube's assumption that hydrogen peroxide captured the nitrosonium ion as fast as it was formed.

This argument says that the nitrosonium ion is specifically reactive towards water, relative to such nucleophiles as amines, hydrazoic acid, or azide and halide ions. This is not true for such reactive cations as the carbonium [6] and chloronium [7] ions. It is difficult to interpret Anbar and Taube's experiments on the reaction between hydrogen peroxide and nitrous acid, but the very high concentrations of hydrogen peroxide (*ca.* 25% w/w) may have had some solvent effect upon the equilibria and rates of both oxygen exchange and the chemical reaction.

The present results show why we obtained a different kinetic law [3] for oxygen exchange between nitrous acid and water from that of others.[2] With no nucleophiles present, other than water and nitrite ions, exchange can occur by reaction (1) and (2) or (3), with rate laws $v = k_3^{NO_2^-}[H^+][NO_2^-][HNO_2] = k_2[HNO_2]^2$, and $v = k[H^+][HNO_2]$ respectively. In our earlier work the concentration of " nitrite " was such that the rate of formation and hydration of dinitrogen trioxide (1) was much greater than any other rate of exchange. From our present results we calculate that exchange by reactions of the nitrous acidium ion would be $<10\%$ of total exchange for M-NO_2^-, and $<20\%$ for 0·5M-NO_2^-.

Anbar and Taube [2] used lower concentrations of nitrite, and here the rates of the two exchange paths are similar. There was also an additional route for exchange, the formation and hydrolysis of a nitrosyl phosphate. This might explain why their rate constants varied with pH and buffer concentration, and why addition of 0·2M-sodium bromide did not affect the exchange rate; there was not enough of it to compete with the other reagents, *i.e.*, water and phosphate ions.

Oxygen exchange between nitric acid and water, catalysed by nitrous acid, has been studied.[8] The rate of xchanege depended on the concentration of " nitrous acid " (by which was meant all of the species present in solution, which on dilution with water can be analysed as nitrous acid) to the first power in 4M-nitric acid, to the second power in 10M-nitric acid, and to the first power in 13M-nitric acid. The rate for a given " nitrous acid " concentration increased with increasing nitric acid concentration. The present results show that the rate of oxygen exchange between " nitrous acid " and water would always be much greater than the observed rate of exchange between nitric acid and water, *i.e.*, the oxygen of the " nitrous acid " was in isotopic equilibrium with the water. This exchange of oxygen atoms between nitrous acid and water cannot be the slow step for the overall exchange. This is of value in eliminating some of the possible mechanisms that could explain results.

Appendix

A relation between the rate of exchange between nitrous acid and water, the rate of the azide–nitrite reaction, and the oxygen-18 content of the nitrous oxide evolved for complete reaction, $N^*_{N_2O}$, when one component is labelled with oxygen-18, can readily be derived as follows.

Reaction conditions are chosen such that the rate equation for chemical reaction contains only a first-order term in nitrite, and such that the acidity and azide concentration remain constant during reaction. This requires a large excess of azide over nitrite, and buffering of the solution with excess of perchloric acid or an azide buffer. The rate equation is therefore:

$$d[NO_2^-]/dt = -d[\text{nitrite}]_4/dt = k'_c[\text{nitrite}]$$

(k'_c is a function of acidity and azide concentration). Integration in the conventional manner gives

$$[\text{nitrite}] = [\text{nitrite}]_0 \exp(-k'_c t)$$

[6] Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603.
[7] de la Mare, Ketley, and Vernon, *J.*, 1954, 1290.
[8] Bunton, Llewellyn, and Halevi, *J.*, 1953, 2653.

If the rate equation for oxygen exchange between nitrous acid and water is also of first order in nitrite, and the tracer is initially in the solvent water

$$v = k'_{E}[\text{nitrite}] = \frac{2[\text{nitrite}][H_2O]}{2[\text{nitrite}] + [H_2O]} \cdot \frac{d \log_e (N_{H_2O} - N_{Nit})}{dt}$$

N_{Nit} = atom % excess of oxygen-18 in the nitrite. This can be rearranged to $N_{Nit} = N_{H_2O}[1 - \exp(\frac{1}{2}k'_{E}t)]$.

The final concentration of nitrous oxide, $[N_2O]_\infty$, is equal to the initial concentration of nitrite, $[\text{nitrite}]_0$. We suppose that the isotopic abundance of the nitrous oxide evolved at any instant is that of the nitrite at that instant, *i.e.*,

$$[N_2O]_\infty N^*_{N_2O} = \int_0^\infty (d[N_2O]/dt) N_{Nit} \cdot dt$$

by substitution we obtain

$$[N_2O]_\infty N^*_{N_2O} = \int_0^\infty N_{H_2O}(d[N_2O]/dt) \cdot dt + \int_0^\infty k'_c[\text{nitrite}]_0 N_{H_2O} \exp[-(k'_c + \tfrac{1}{2}k'_{E})t] \cdot dt$$

These integrals can readily be evaluated by standard procedures, and rearrangement of the resulting expression leads to the equation

$$\frac{N^*_{N_2O}}{N_{H_2O} - N^*_{N_2O}} = \frac{k'_{E}}{2k'_c}$$

A number of assumptions have been made in the derivation of this expression, and these will now be considered.

(i) It has been tacitly assumed that isotope effects can be neglected. This assumption is commonly made in studies of the kinetics of oxygen-exchange reactions with oxygen-18 as tracer, and does not appear to introduce a significant error. (ii) It has been assumed that N_{H_2O} remains constant during the exchange; this is justified because in the present work there was always at least a 500-fold excess of oxygen in the form of water over oxygen in the form of nitrite. (iii) The rate equation for chemical reaction was taken as $v = k'_c[\text{nitrite}]$. The kinetic studies described in Parts I and II [1] show that the rate equation under the conditions of the present study is of the first order in nitrite. In all experiments save one (No. 50, Table 3) there was at least a tenfold excess of azide over nitrite, and in all cases there was a large excess of buffering agent over nitrite save in experiment 19, Table 1. (iv) It has been assumed that reaction was complete when the nitrous oxide was removed for isotopic analysis. In all experiments the reacting solutions were left for at least ten half-lives of decomposition before removing the nitrous oxide. There is no exchange between water and nitrous oxide.[9]

Experimental

Materials.—Water enriched in oxygen-18, obtained by fractional distillation of water, was purified by distillation from alkaline permanganate. Sodium nitrite enriched in oxygen-18 was obtained by exchange of the isotopically normal salt with [^{18}O] water of *ca.* 2% enrichment.[3] The preparation and purification of the other materials have already been described.[1b]

Isotopic Experiments.—The two solutions were placed in the arms of a Y tube, and frozen by cooling in liquid air. The tube was pumped out, and the frozen solution allowed to warm and melt. The tube was then immersed in an ice–water bath until temperature equilibrium was attained. The contents of the two arms were then rapidly mixed, and the tube kept at 0° for at least ten half-lives. The solutions were again frozen in liquid air, and all non-condensable gas pumped off. The tubes were then allowed to warm and the nitrous oxide was transferred to another vessel, and stored over concentrated sodium hydroxide solution. This removed any small amounts of carbon dioxide; these would interfere with the mass-spectrometric analysis

[9] Friedman and Bothner-By, *J. Chem. Phys.*, 1952, **20**, 4591.

XUM

of nitrous oxide. The abundance of oxygen-18 in the nitrous oxide was determined from the relative intensities of the peaks of mass number 44 and 46.

Anbar and Taube have reported that when solutions of sodium nitrite and sodium azide are acidified there is much extraneous exchange between nitrite and solvent.[3] We had similar difficulties. For the decompositions carried out in azide buffers it was necessary to put a solution of isotopically normal sodium nitrite in normal water in one arm of the Y tube, while the enriched water was in the other arm. If the initially normal nitrite was dissolved in enriched water at the start of the experiment, inconsistent results were obtained. This effect was in part due to spraying from one arm to the other during the freezing down and melting processes; also the volatile hydrazoic acid may have distilled over. Both these effects would acidify the sodium nitrite solution, and cause exchange, before the main bulks of the two solutions were mixed. Another effect that might account for some of the inconsistent results is that addition of acid to a solution of sodium nitrite and azide could cause local high concentration of acid and increase the rate of exchange. The work described above has shown that the ratio of exchange rate to reaction rate is much higher in excess of perchloric acid ($[H^+]$ *ca.* 0·2M) than in azide buffers ($[H^+]$ *ca.* 10^{-5}M).

In the experiments with excess of perchloric acid and isotopically normal water these difficulties were not encountered. For these, perchloric acid was in one arm of the Y tube, and enriched sodium nitrite and sodium azide in normal water in the other. The solutions were degassed without freezing, to prevent spraying. Perchloric acid is involatile in dilute aqueous solution, so that there was no distillation from one arm to the other. On mixing the solutions any local concentration of acid was not much higher than those in the final solution, and so the ratio of exchange to chemical reaction was not seriously affected. The final justification for the validity of these methods is to be found in the good agreement between the rate of the nitrous acid–water exchange obtained from reaction in azide buffers at pH 4—5, in excess of perchloric acid at pH 1—2, and from the direct measurements of the exchange rate which make no assumptions about the mechanism of the azide–nitrite reaction, but use it essentially as an empirical analytical method.

The authors are indebted to Professor E. D. Hughes, F.R.S., and Sir Christopher Ingold, F.R.S., for their interest and to Dr. J. H. Ridd for many valuable discussions.

William Ramsay and Ralph Forster Laboratories,
University College, Gower St., London, W.C.1. [*Received, April 27th,* 1959.]

---

700. *Comparison of Some Properties of Anhydrous Sulphuric Acid and Dideuterosulphuric Acid over a Range of Temperature.*

By N. N. Greenwood and A. Thompson.

Anhydrous dideuterosulphuric acid has been prepared and its properties have been compared with those of sulphuric acid. Substitution of deuterium for hydrogen raises the m. p. and density of the compound, leaves the molar volume and viscosity almost unchanged, and lowers the specific electrical conductivity. The activation energies of viscous flow and electrical conduction are almost identical, and neither is affected by deuterium substitution. The conductivity decreases more than 300-fold on solidification though this factor is markedly dependent on the purity of the acid. These results are compared with those observed for deuterium substitution in other systems and the effects are discussed in terms of the proton-jump theory of electrical conduction in sulphuric acid.

Two of the most characteristic features of anhydrous sulphuric acid are its self-dissociation into ionic products [1] and its ability to conduct electricity by a proton-switch mechanism.[2] These factors combine to give sulphuric acid a higher electrical conductivity at room temperature than any other compound except nitric, phosphoric, and selenic acids and the

[1] Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1933, **55**, 1900.
[2] Hammett and Lowenheim, *ibid.*, 1934, **56**, 2620.

hydrates of boron trifluoride. The cryoscopic and thermodynamic consequences of self-dissociation of a solvent by autoprotolysis and ionic dehydration are now well established but, despite numerous experimental and theoretical investigations, there remains some uncertainty about the factors which facilitate electrical conduction by a chain mechanism involving proton jumps. Indeed, it is still difficult to predict whether a given solvent will show abnormal conduction or not. No theory is completely successful in interpreting why the solvated hydrogen ion has an anomalous mobility in water,[3] methanol,[4,5] ethanol,[4] and anhydrous sulphuric acid [6] but not in liquid ammonia, hydrogen fluoride, or ethylene glycol, and why the anions characteristic of the solvents water, sulphuric acid, and possibly hydrogen fluoride [7] (OH^-, HSO_4^-, and F^-) have abnormally high mobilities whereas those characteristic of methanol, ethanol, and ammonia (OMe^-, OEt^-, NH_2^-) have not. Nor do the theories agree on whether the rate-determining process in water is (i) the frequency of proton jumps over a potential energy barrier, (ii) the quantum-mechanical tunnelling frequency through the barrier, (iii) the prior reorientation of the ion and solvent molecule into positions which facilitate the proton transfer, or (iv) the subsequent rotation of the molecule after proton transfer into a position favourable for the next transfer.[8,9]

Because of the difficulties involved in developing a satisfactory theory of abnormal ionic mobilities for water itself and the still more formidable problem of extending such a theory to other solvents, it seemed that further understanding of these effects might come more readily from an experimental approach which extended the number of liquids showing abnormal conduction and which investigated the effect of substituting hydrogen by deuterium in these systems. As a result of such work, phosphoric acid [10] and selenic acid can now be added to the above list of four compounds which conduct by a proton-jump mechanism, and this paper reports results of the complementary study of the influence which deuterium substitution has on the electrical and other physical properties of sulphuric acid. The measurements were made over a wide range of temperature to enable activation energies to be calculated and to determine how these energies varied with temperature. During the course of this work an independent study of some properties of dideutero-sulphuric acid at its m. p. and at two other temperatures was published;[11] where the two investigations overlap there is substantial agreement on the properties of dideuterosulphuric acid.

Experimental and Results

Sulphuric acid was prepared and handled on the same scale as, and in apparatus identical with, that used for dideuterosulphuric acid. This had the double advantage of (i) proving the reliability of the experimental techniques by reproducing the most accurate published data on sulphuric acid, and (ii) increasing the precision of comparison of the two compounds by eliminating the effect of slight errors in the absolute values of calibration constants.

The anhydrous acids were prepared on a 30 g. scale in a vacuum line by transferring the stoicheiometric amount of water or heavy water on to a known weight of sulphur trioxide which had previously been purified by repeated distillation *in vacuo*.[12] One batch of sulphuric acid was also prepared by titrating "AnalaR" sulphuric acid with dilute oleum until a minimum in conductivity was obtained. The results on the two samples were the same to within experimental error.

Electrical conductivity was measured after the acids had been subjected to final purification by repeated fractional freezing under vacuum in an all-glass apparatus attached directly to

[3] Danneel, *Z. Elektrochem.*, 1905, **11**, 249.
[4] Uhlich, *Trans. Faraday Soc.*, 1927, **23**, 288; Walden, *Z. phys. Chem.*, Bodenstein Festband, 1931, 19.
[5] Hartley and Raikes, *Trans. Faraday Soc.*, 1927, **23**, 393.
[6] Gillespie and Wasif, *J.*, 1953, 209.
[7] Kilpatrick and Lewis, *J. Amer. Chem. Soc.*, 1956, **78**, 5186.
[8] Conway, Bockris, and Linton, *J. Chem. Phys.*, 1956, **24**, 835, and refs. therein.
[9] Eigen and de Maeyer, *Proc. Roy. Soc.*, 1958, **247**, *A*, 505.
[10] Greenwood and Thompson, following paper.
[11] Flowers, Gillespie, Oubridge, and Solomons, *J.*, 1958, 667.
[12] Greenwood and Thompson, "Inorganic Syntheses," Vol. VI, in the press.

the conductivity cell. In this process the acid was reduced to about one-tenth of its original volume. Two independent concordant sets of results were obtained on using cells with bright platinum electrodes. The cell constants were 85·33 cm.$^{-1}$ and 48·15 cm.$^{-1}$. The cell resistances, which were of the order of 10^3—10^4 ohm, were measured with a precision of about 1 part in 3000 on an earthed A.C. network at 1000 cycles/sec.[13] Variation of frequency from 500 to 3000 cycles/sec. left the resistance unchanged and results were reproducible during several thermal cycles up to 70°.

Viscosity was measured in a sealed glass viscometer which used the Wier principle to maintain a constant mean head of liquid over a range of temperature.[14] It was calibrated with aniline and 60% aqueous sucrose solution by means of an intermediate viscometer, and the kinematic viscosity (ν cs) was found to be related to the outflow time (t sec.) by the equation $\nu = \eta d^{-1} = 0{\cdot}0840t - 6{\cdot}56t^{-1}$. Here η (cP) is the dynamic viscosity and d (g.ml.$^{-1}$) the density. Because of the difficulties inherent in the measurement of the absolute viscosity of highly viscous liquids it would be rash to claim more than 1% for the absolute accuracy of these measurements but the relative viscosity of the two compounds and their comparative values at different temperatures are precise to 2 parts per thousand.

Density, which was corrected for buoyancy of the air, was measured in a Pyrex-glass dilatometer having a volume of 11·7 ml. and a capillary radius of 1 mm. Temperatures were measured on N.P.L. calibrated mercury-in-glass thermometers; the accuracy on an absolute scale was ±0·02° and the precision with which a given temperature could be reproduced was ±0·005°.

Results.—The m. p. of our anhydrous sulphuric acid was 10·35° ± 0·02°, close to the accepted value of 10·371°.[15] The highest m. p. observed for dideuterosulphuric acid was 14·10°, but an extrapolation of the values obtained as a function of the number of fractional crystallisations indicates a limiting value somewhere between 14·3° and 14·4°, in agreement with the recently published value of 14·35° ± 0·02° which was obtained in experiments using a larger initial volume of acid.[11]

The density (d_4^t), dynamic viscosity (η), and specific conductivity (κ) of the two acids were determined at 5° intervals from 10° to 60° and typical results are summarized in Table 1. The conductivity was also measured at 7·5° and 70° but viscosities at these temperatures (in parentheses) were found by extrapolation

Values of the molar conductivity ($\mu = \kappa V_M$) and reduced conductivity ($\mu\eta$) given in the last four columns of Table 1 will be mentioned in the Discussion.

Density varied linearly with temperature (t°):

$$H_2SO_4\text{: } d_4^t = 1{\cdot}8516 - 1{\cdot}000 \times 10^{-3}t\text{; } D_2SO_4\text{: } d_4^t = 1{\cdot}8816 - 0{\cdot}980 \times 10^{-3}t$$

TABLE 1. *Density, viscosity, and conductivity between 7·5° and 70°.*

Temp.	d_4^t (g. cm.$^{-3}$)		η (cP)		$10^3\kappa$ (ohm^{-1} cm.$^{-1}$)		μ (ohm^{-1} cm.^{2} mole^{-1})		$\mu\eta$ (ohm^{-1} cm.^{2} cP mole^{-1})	
	H_2SO_4	D_2SO_4	H_2SO_4	D_2SO_4	H_2SO_4	D_2SO_4	H_2SO_4	D_2SO_4	H_2SO_4	D_2SO_4
7·5°	1·8441	1·8743	(50·1)	(51·5)	0·5166	0·1440	0·2746	0·0738	(13·76)	(3·80)
10·0	1·8416	1·8718	44·88	45·65	0·5769	0·1598	0·3071	0·0854	13·78	3·90
15·0	1·8359	1·8670	36·07	37·79	0·7110	0·1948	0·3795	0·1046	13·70	3·84
20·0	1·8318	1·8620	29·56	30·08	0·8671	0·2351	0·4641	0·1263	13·72	3·80
25·0	1·8267	1·8572	24·55	24·88	1·044	0·2832	0·5602	0·1524	13·74	3·79
30·0	1·8212	1·8522	20·62	20·74	1·242	0·3356	0·6681	0·1812	13·77	3·76
35·0	1·8162	1·8473	17·24	17·44	1·465	0·3963	0·7903	0·2146	13·63	3·74
40·0	1·8117	1·8422	14·67	14·87	1·712	0·4637	0·9260	0·2517	13·59	3·75
45·0	1·8066	1·8373	12·62	12·81	1·985	0·5425	1·072	0·2952	13·54	3·78
50·0	1·8017	1·8324	10·93	11·12	2·279	0·6243	1·239	0·3407	13·56	3·79
60·0	1·7921	1·8228	8·50	8·55	2·929	0·8079	1·602	0·4433	13·61	3·79
70·0	1·7816	1·8134	(6·78)	(6·79)	3·683	1·0280	2·025	0·5558	(13·70)	(3·78)

The usual activation energy plots of log κ, log μ, and log η *versus* $1/T$ (°K) were curved, but when $1/T^2$ was used as abscissa the plots were linear, indicating that the data can be represented by equations of the form:

$$\kappa = \kappa_0 \exp(-C_\kappa/RT^2)\text{; } \mu = \mu_0 \exp(-C_\mu/RT^2)\text{; } \eta = \eta_0 \exp(C_\eta/RT^2)$$

[13] Greenwood and Worrall, *J. Inorg. Nuclear Chem.*, 1957, **3**, 357.
[14] Greenwood and Wade, *ibid.*, p. 349; *J. Sci. Instr.*, 1957, **34**, 288.
[15] Gable, Betz, and Maron, *J. Amer. Chem. Soc.*, 1950, **72**, 1445; Kunzler and Giauque, *ibid.*, 1952, **74**, 5271.

The validity of these equations is illustrated in Fig. 1, the values of the constants being summarized in Table 2. The most striking feature of these results is the great similarity in the 6 values of the exponential constant C. It will be shown later that this implies a similarity in the activation energies of the various processes occurring.

The conductivity of solid sulphuric acid was less than that of the supercooled liquid by a factor which depended on the purity of the acid and on the temperature of comparison. Fig. 2 illustrates that, whilst small amounts of water have comparatively little effect on the conductivity of the liquid, they increase the conductivity of the solid by nearly two orders of magnitude at 7°. Hence, at this temperature, the ratio of the conductivity of the supercooled liquid to that of the solid, which was 310 for the pure acid, decreased to 116, 82, 39, 10, and 6·6 for the five concentrations of water indicated in Fig. 2. At 10° the conductivity of the liquid was 68·3

FIG. 1. *Conductivity and fluidity of H_2SO_4 and D_2SO_4.*

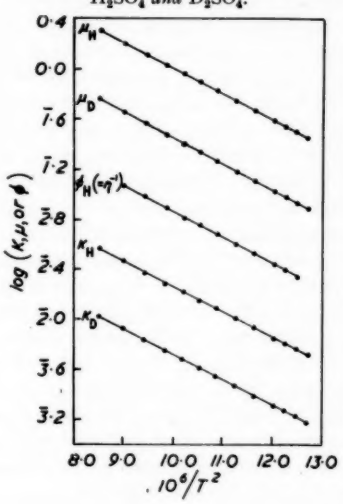
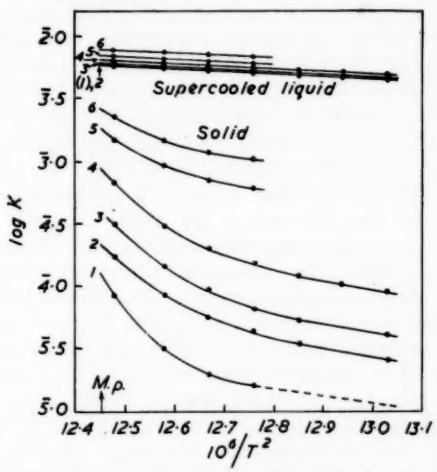


FIG. 2. *Conductivity of solid and supercooled sulphuric acid between 3° and 10° as a function of concentration.*



1, Anhydrous H_2SO_4; 2, 8 mmoles of H_2O per kg. of soln.; 3, 13 mmoles of H_2O per kg. of soln.; 4, 20 mmoles of H_2O per kg. of soln.; 5, 26 mmoles of H_2O per kg. of soln.; 6, 36 mmoles of H_2O per kg. of soln.

times that of the solid but this factor dropped to 3·5 for acid containing 36 millimoles of water per kg. of solution. (Concentrations of water were estimated by measuring the specific conductivity at 25·0° and then interpolating from recent precise data relating the conductivity to water content.[16]) The curves for solid sulphuric acid showed a premelting increase in conductivity very similar to that observed for ice,[17] and at 10° (0·35° below the m. p.) there was

TABLE 2. *Conductivity and viscosity constants.*

Constant	H_2SO_4	D_2SO_4	Constant	H_2SO_4	D_2SO_4
κ_0 (ohm^{-1} cm.$^{-1}$)	1·990	0·543	C_κ (kcal. deg. mole^{-1})	927	928
μ_0 (ohm^{-1} cm.^{2} mole^{-1})	121·5	32·75	C_μ (kcal. deg. mole^{-1})	950	950
η_0 (cP)	0·1066	0·1068	C_η (kcal. deg. mole^{-1})	960	963 *

* Varies from 990 at 10° to 937 at 60°.

also a slow drift to higher conductivities, the equilibrium value being approached after about 1 hr. During this process there was no visible sign of melting. Below 7° the curves became almost linear; the slope was virtually independent of water content and corresponded to an exponential constant $C_\kappa \sim 2910$ kcal. deg. mole.$^{-1}$ (cf. liquid: $C_\kappa = 927$ kcal. deg. mole.$^{-1}$; ratio 3·14).

[16] Gillespie, Oubridge, and Solomons, *J.*, 1957, 1804.
[17] Bradley, *Trans. Faraday Soc.*, 1957, **53**, 687.

Discussion

Three general aspects of the results arise for discussion: (i) The absolute values of the density, viscosity, and conductivity of sulphuric acid, and a comparison of these with values in the literature. (ii) The influence of deuterium substitution on the properties of sulphuric acid as compared with the effect of isotopic substitution in other systems. (iii) The temperature variation of viscosity and conductivity and the interpretation of the activation energies of viscous flow and electrical conduction. These points are best considered by discussing the density, viscosity, and conductivity separately [sections (i), (ii), (iii)]. The results are relevant to theories on the mechanism of electrical conduction in sulphuric acid [section (iv)] and, in particular, the proton-jump theory is examined. Implications of the conductivity of solid sulphuric acid [section (v)] are also discussed.

(i) *Density.*—The industrial and economic importance of sulphuric acid ensured the early determination of accurate values for the density as a function of temperature and composition. Nearly a century ago Marignac [18] represented the density of the anhydrous acid as $d_4^t = 1{\cdot}85289 - 0{\cdot}0010654t + 0{\cdot}00000132t^2$; this differs from our values by 7 parts in 10^4 at 0° and by only 2 parts in 10^4 at 25°. Little point would be served in enumerating the many intervening concordant determinations but a recent precise value [19] of $d_4^{25} = 1{\cdot}8269$ can be mentioned to illustrate the agreement with our value of $d_4^{25} = 1{\cdot}8267$. The density of dideuterosulphuric acid ($d_4^{25} = 1{\cdot}8572$) is 1·64% greater, and agrees closely with the only published value [11] for this compound, $d_4^{25} = 1{\cdot}8573$. The equations on p. 3476 can therefore be taken to represent the density accurately between 0° and 70°.

Of more interest is the molar volume. Deuterium substitution almost invariably increases the molar volume of a liquid, the only two exceptions being the special case of deuterium itself, whose molar volume at −253° is 12·9% less than that of liquid hydrogen because of a zero-point energy effect,[20] and hexadeuterobenzene where the change in molar volume compared with benzene at 25° is −0·21%.[21] For all other isotopic pairs of liquids investigated deuterium substitution causes only a very slight increase in molar volume. At 25° the molar volumes of the two sulphuric acids are $53{\cdot}69_0$ and $53{\cdot}89_2$ ml. mole^{-1}, the increase being $0{\cdot}20_2$ ml. (0·38%). This is unexpectedly large, since the deuterium atom is the same size as the hydrogen atom and, in the gas phase, bond distances involving the two isotopes are virtually identical. Differences in the molar volumes of isotopic pairs of liquids must therefore be ascribed primarily to differences in intermolecular forces rather than to differences in molecular size. For non-hydrogen-bonded liquids at 20° the increase in molar volume of a deutero-compound compared with its hydrogen analogue seems to be less than 0·1%; *e.g.*, tetradeuterothiophen, C_4D_4S, 0·0%,[22] deuterochloroform, $CDCl_3$, 0·07%,[23] boron trifluoride dideuterate, $D_3O[BF_3{\cdot}OD]$, 0·08%,[24] boron trifluoride monodeuterate, $D[BF_3{\cdot}OD]$, 0·1%,[25] tetrachlorodideuteroethane, $(CDCl_2)_2$, 0·1%.[26] On the other hand, when strong hydrogen bonding contributes to the liquid structure the increase in molar volume attending deuteration is significantly larger. Deuterium peroxide, D_2O_2, appears to be an intermediate case (increase at 20°, 0·13% [27]), but for heavy water the increase at 25° is 0·38%,[28] which is similar to the value found for dideuterosulphuric acid

[18] Landolt–Börnstein, " Physikalisch-Chemische Tabellen," 5th Edn., 1923, p. 307.
[19] Gillespie and Wasif, *J.*, 1953, 215.
[20] Itterbeck and Paemel, *Physica*, 1941, **8**, 133.
[21] Ingold, Raisin, Wilson, Bailey, and Topley, *J.*, 1936, 915; see also Klit and Langseth, *Z. phys. Chem.*, 1936, *A*, **176**, 65 (−0·22% at 20°); Bowman, Benedict, and Taylor, *J. Amer. Chem. Soc.*, 1935, **57**, 960 (−0·07% at 25°); Erlenmeyer, Lobeck, Gartner, and Epprech, *Helv. Chim. Acta*, 1936, **19**, 336 (−0·04% at 20°).
[22] Steinkopf and Böetius, *Annalen*, 1941, **546**, 208.
[23] Breuer, *J. Amer. Chem. Soc.*, 1935, **57**, 2236.
[24] Greenwood, *J. Inorg. Nuclear Chem.*, 1958, **5**, 229.
[25] *Idem, ibid.*, p. 224.
[26] Breuer, *J. Amer. Chem. Soc.*, 1936, **58**, 1289.
[27] Phibbs and Giguère, *Canad. J. Chem.*, 1951, **29**, 173.
[28] Stokland, Ronaess, and Tronstad, *Trans. Faraday Soc.*, 1939, **35**, 312; Wirtz, *Phys. Z.*, 1942, **43**, 465.

at the same temperature (0·38%), and for trideuterophosphoric acid, D_3PO_4, the molar volume is 0·93% higher than for normal phosphoric acid.[9] It is tempting to conclude that the deuterium bridge is longer than the hydrogen bridge in these liquids.[29] Moreover, since the temperature coefficient of the density of dideuterosulphuric acid is less than that of sulphuric acid, the disparity in molar volume decreases with rise in temperature and is only 0·24% at 70°. A similar decrease is observed with water and implies that the degree of hydrogen bonding diminishes as the temperature rises. This is consistent with the concurrent decrease in activation energy of viscous flow to be discussed in the next section.

(ii) *Viscosity.*—The viscosity of anhydrous sulphuric acid at 25° has only recently been determined accurately and no reliable data exist on the variation of viscosity with temperature. The following values appear in the literature for η_{25} though not all refer to precisely 100·0% acid: 19·15,[30] 19·85,[31] 23·5,[32] 23·57,[33] 24·0,[34] 24·19,[35] 24·20,[36] 24·68,[37] 24·77,[38] and 25·33.[39] To these have recently been added two others, 24·53 [40] and 24·54,[19] in excellent agreement with our value of 24·55 cP, and it is recommended that this be accepted as the viscosity of anhydrous sulphuric acid at 25°. The literature is equally confused about values at other temperatures. This is illustrated in Table 3 which summarizes values at even temperatures between 10° and 60° and, as values at other temperatures show a similar spread, no reliable deductions could previously be made about the detailed dependence of viscosity on temperature. The present measurements resolve this difficulty and give a consistent set of values over a range of 50°. The viscosity of dideuterosulphuric acid, which had not previously been recorded, was measured over the same temperature range.

TABLE 3. *Viscosity (in* cP*) of sulphuric acid at selected temperatures.*

Temp.	This work	Lutschinski [a]	Other values
10·0°	44·88	—	35·17 [b]
20·0	29·56	25·4	21·93,[c] 24·22,[b] 28·21,[d] 28·40 [d]
30·0	20·62	15·68	19·69,[d] 19·84,[d] 21·34 [e]
40·0	14·67	11·45	13·07,[b] 14·80 [f]
50·0	10·93	8·82	10·55,[g] 10·6,[h] 10·69,[d] 10·78,[d] 10·80 [i]
60·0	8·50	7·22	8·32,[j] 8·78 [k]

[a] Ref. 31. [b] Bingham and Stone, *J. Phys. Chem.*, 1923, **27**, 701. [c] Graham, *Phil. Trans.*, 1861, **151***A*, 373. [d] Schwab and Kolb, *Z. phys. Chem.* (*Frankfurt*), 1955, **3**, 52. [e] Pound, *J.*, 1911, **99**, 708. [f] Tutunzic and Liler, *Bull. Soc. chim. Belgrade*, 1953, **18**, 521. [g] Ref. 34. [h] Ref. 32. [i] Ref. 36. [j] Ref. 37. [k] Ref. 38.

The viscosity of sulphuric acid as a function of temperature can be represented accurately by the expression $\eta = \eta_0 \exp(C_\eta/\boldsymbol{R}T^2)$. This implies that the activation energy E_η varies inversely as the absolute temperature because

$$\log \eta = \log \eta_0 + \frac{C_\eta}{2{\cdot}303\boldsymbol{R}}\left(\frac{1}{T}\right)^2$$

hence

$$\frac{\mathrm{d}(\log \eta)}{\mathrm{d}(1/T)} = \frac{2C_\eta}{2{\cdot}303\boldsymbol{R}} \cdot \frac{1}{T} = \frac{E_\eta}{2{\cdot}303\boldsymbol{R}}$$

Further, $\dfrac{\mathrm{d}(\log \eta)}{\mathrm{d}(1/T^2)} = \dfrac{C_\eta}{2{\cdot}303\boldsymbol{R}}$, so that $E_\eta = 2C_\eta/T$.

[29] Wirtz, *Z. Elektrochem.*, 1958, **62**, 389.
[30] Bergius, *Z. phys. Chem.*, 1910, **72**, 338.
[31] Lutschinski, *ibid.*, 1934, *A*, **169**, 269.
[32] Dunstan, *Proc. Chem. Soc.*, 1914, **30**, 104.
[33] Schwab, *Chem. Ber.*, 1957, **90**, 221.
[34] Rhodes and Hodge, *Ind. Eng. Chem.*, 1929, **21**, 142.
[35] Tutunzic, Liler, and Kosanovic, *Bull. Soc. chim. Belgrade*, 1955, **20**, 363.
[36] Rhodes and Barbour, *Ind. Eng. Chem.*, 1923, **15**, 850.
[37] Dunstan and Wilson, *J.*, 1907, **91**, 85, as corrected in ref. 32.
[38] Bright, Hutchison, and Smith, *J. Soc. Chem. Ind.*, 1946, **65**, 385.
[39] Brun, *Univ. i Bergen Årbok*, 1952, *Naturvitenskap. Rekke* No. 12, 1953, 1.
[40] Hetherington, Nichols, and Robinson, *J.*, 1955, 3141.

XUM

The activation energy at any temperature is therefore best computed by first plotting $\log \eta$ as a function of $1/T^2$ (Fig. 1) to obtain C_η (Table 2), and then applying the relation $E_\eta = 2C_\eta/T$, rather than by plotting $\log \eta$ against $1/T$ and drawing a tangent to the curve at the required temperature. Activation energies calculated in this way for three temperatures are listed in the last two columns of Table 4 which show clearly the decrease in

TABLE 4. *Activation energies for viscous flow and electrical conduction.*

	E_κ (kcal. mole^{-1})		E_μ (kcal. mole^{-1})		E_η (kcal. mole^{-1})	
Temp.	H_2SO_4	D_2SO_4	H_2SO_4	D_2SO_4	H_2SO_4	D_2SO_4
10°	6·55	6·55	6·71	6·71	6·78	6·99
25	6·22	6·22	6·37	6·37	6·44	6·64
60	5·56	5·57	5·70	5·70	5·76	5·62

energy as the temperature rises. Normally the process which requires the smaller activation energy predominates at lower temperatures and the opposite trend for the activation energy of viscous flow in sulphuric acid implies some structural change in the liquid (such as the progressive breaking of hydrogen bonds) which increasingly facilitates the flow of the liquid as the temperature is raised. A similar effect is well known for water, although for that liquid $\log \eta$ is a linear function of $1/T^2$ only above 20°, the slope at lower temperatures increasing by about 7%.

If the decrease in the activation energy of viscous flow arises from a gradual reduction in the extent of hydrogen bonding, then the average size of the flow units involved in the transfer of momentum from one shear layer to the next will progressively diminish. This should be paralleled by a decrease in the value of Batschinski's constant B, since the magnitude of this constant (which is obtained from the relation $v = b + B\phi$ between specific volume, v, and fluidity, ϕ) is roughly proportional to the size of the kinetic units of flow in a liquid.[24] Such a decrease is, in fact, observed, the value of B falling from 0·28 CP ml. g.$^{-1}$ at 10° to 0·21 at 25° and 0·11 at 60°. The values for dideuterosulphuric acid are slightly smaller, being 0·26, 0·19, and 0·10 CP ml. g.$^{-1}$ at the same temperatures. On the assumption of direct proportionality between Batschinski's constant and the size of flow units, the figures suggest that the size of these structural units in sulphuric acid is halved when the temperature is raised from 25° to 60°.

The kinematic viscosity (ν) of the two compounds is the same to within experimental error, so that the difference in dynamic viscosity ($\eta = \nu d$) is due solely to the difference in density of the two liquids. At 25° the ratio of the dynamic viscosity of dideuterosulphuric acid to that of sulphuric acid itself is 1·014, which is a smaller ratio than for any other of the eight isotopic pairs of liquids yet investigated.[24,9,41] Again, deuterium substitution invariably increases the activation energy of viscous flow.[24,9,41] Whilst Table 4 indicates that this is also true for the present compounds, at least at the lower temperatures, the increase is probably not far outside experimental error, since the exponential constants C_η given in Table 2 differ by only 0·3%. Indeed, the main effect of deuteration seems to be the introduction of a slight non-linearity in the relation between $\log \eta$ and $1/T^2$.

(iii) *Conductivity.*—There is now general agreement that the conductivity of anhydrous sulphuric acid at 25° is $1{\cdot}044 \times 10^{-2}$ ohm^{-1} cm.$^{-1}$ as found in this work. The most precise figure in the literature [16] is $1{\cdot}0439 \pm 0{\cdot}0005 \times 10^{-2}$, which is identical with our value, and other recent determinations give $1{\cdot}045 \times 10^{-2}$ [42,43] and $1{\cdot}046 \times 10^{-2}$.[39] This variation may well represent a difference in calibration of temperature scales in the various laboratories since Table 1 indicates that $0{\cdot}001 \times 10^{-2}$ ohm^{-1} cm.$^{-1}$ is equivalent to a temperature change of 0·002°. The older literature on the conductivity of sulphuric acid at 25° has been reviewed several times [16,39,43,44] and requires no further comment. Less is known, however,

[41] Greenwood and Thompson, *J.*, 1959, 3493.
[42] Trenner and Taylor, *J. Phys. Chem.*, 1931, **35**, 1336.
[43] Hetherington, Hub, Nichols, and Robinson, *J.*, 1955, 3300.
[44] Gillespie and Wasif, *J.*, 1953, 204.

about the temperature variation of the conductivity, the only measurements on reliable acid at temperatures other than 25° being at 9·66° and 40° where the values were 0·570 × 10^{-2} and 1·711 × 10^{-2} ohm^{-1} cm.$^{-1}$, respectively, compared with our values of 0·569 × 10^{-2} and 1·712 × 10^{-2} ohm^{-1} cm.$^{-1}$ at the same temperatures.

Only one report of the conductivity of dideuterosulphuric acid has been published,[11] the values of $10^2\kappa$ (ohm^{-1} cm.$^{-1}$) at 10°, 25°, and 40° (compared with our values in parentheses) being 0·133 (0·1598), 0·2568 (0·2832), and 0·446 (0·4637). This suggests [11] that the dideuterosulphuric acid used in the present work contained 0·09 mole % excess of heavy water. Both sets of figures agree, however, that substitution of deuterium for hydrogen results in a substantial reduction in the electrical conductivity of sulphuric acid. Furthermore, the discrepancy in absolute values is unlikely to affect values of the temperature coefficient significantly, since Fig. 2 shows that the presence of even 0·36 mole % of water in sulphuric acid (curve 6) has but slight effect on the slope of the curve.

Treatment of the conductivity data in Table 1 by the methods used for viscosity in the preceding section leads to the conclusion that the activation energy for conduction in both acids varies inversely as the absolute temperature, *i.e.*, $E_\kappa = 2C_\kappa/T$. Values for these activation energies, and for the activation energy of molar conduction ($\mu = \kappa V_M$), are given in Table 4. The similarity at each temperature between values of E_μ and E_η for both compounds is particularly noteworthy. Usually,[45] such similarity is taken to imply that ionic migration is viscosity-controlled, the mobility of the ions being inversely proportional to viscosity as required by Stokes's law. Such an interpretation is at variance with the known mechanism of conduction in sulphuric acid which takes place predominantly by proton jumps rather than by normal ionic migration.[2,6,46] This problem is considered further in the next section.

(iv) *Mechanism of Electrical Conduction.*—In general, the magnitude of the electrical conductivity of an ionizing protonic solvent depends both on the extent of self-dissociation and on the mobility of the ions so formed. The mobility has two components, the normal Kohlrausch migration velocity and an excess of mobility due to a proton-jump mechanism. Increase in temperature alters the concentration of ions and also their mobility (by altering the viscosity and the extent of hydrogen bonding). Similarly, substitution of hydrogen by deuterium can affect the extent of self-dissociation as well as the viscosity and the extent and strength of hydrogen bonding. It is remarkable, therefore, that the activation energy of conduction in sulphuric acid (which reflects changes both in the number and in the mobility of the ions) should so exactly parallel the activation energy of viscous flow. It is still more remarkable that deuterium substitution, which lowers both the concentration of ions and their mobility, should also leave the activation energies unchanged. Various interpretations of these observations can be considered by examining in detail the factors contributing to the conductivity. If n_+ and n_- are the number of cations and anions per ml. formed by autoprotolysis ($2H_2SO_4 \rightleftharpoons H_3SO_4^+ + HSO_4^-$), and v_+ and v_- are the mobilities of these ions, then

$$\kappa = n_+ev_+ + n_-ev_- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

For the pure, anhydrous acid $n_+ = n_-$ ($=n$, say) and, since the minimum in the conductivity–composition plot occurs almost exactly at the stoicheiometric ratio H_2O,SO_3,[16,47] it follows that the mobilities of the two ions are very similar (*i.e.*, $v_+ = v_- = v$, say). Hence $\kappa = 2nev$. Further, $n = \sqrt{K_{ap}}$, where the autoprotolysis constant $K_{ap} = [H_3SO_4^+][HSO_4^-]$, so that

$$\kappa = 2ev\sqrt{K_{ap}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

[45] Greenwood and Martin, *J.*, 1953, 1427.
[46] Gillespie and Wasif, *J.*, 1953, 221.
[47] Kunzler and Giauque, *J. Amer. Chem. Soc.*, 1952, **74**, 804.

XUM

By taking logarithms and differentiating with respect to $1/T$, one arrives at the relation

$$E_\kappa = \tfrac{1}{2}\Delta H_{ap} + E_v \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where E_κ is the activation energy for conduction, E_v is the activation energy for ionic migration, and ΔH_{ap} is the heat of autoprotolysis.

The following three interpretations of the similarities in the activation energies shown in Table 4 can be considered. (*a*) Sulphuric acid is completely dissociated into ions so that, by eqn. (1), changes in conductivity are due entirely to changes in ionic mobility. It follows that E_κ must equal E_v and, since E_κ is very similar to E_η, the activation energies of viscosity and ionic migration must also be almost equal. This implies that mobility is inversely proportional to viscosity (Walden's rule) and suggests normal ionic migration. Under such conditions the mobility of an ion is relatively insensitive to its mass (cf. the small range of ionic mobilities in water) and substitution of hydrogen by deuterium would leave the mobility and the activation energy of migration substantially unchanged, as observed. Furthermore, since the molar volume of sulphuric acid at 25° is 53·7 cm.^{3}, the calculated number of ions per cm.^{3} for complete dissociation is $1{\cdot}12 \times 10^{22}$; substitution of this figure, together with the value for the conductivity ($\kappa = 1{\cdot}044 \times 10^{-2}$ ohm^{-1} cm.$^{-1}$) and the value of e ($1{\cdot}59 \times 10^{-19}$ coulomb), in equation (1) leads to an ionic mobility of $5{\cdot}84 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1}. This is of the same order of magnitude as the experimentally determined mobility of the hydrogen sulphate ion:[46] $\sim 150/F = 15{\cdot}6 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1}. However, this interpretation cannot be accepted as it is completely at variance with the cryoscopically determined degree of ionic dissociation[48] which gives $K_{ap} = 1{\cdot}7 \times 10^{-4}$ g.-ion^2 kg.$^{-1}$ and $[HSO_4^-] = 0{\cdot}013$ molal, *i.e.*, $8{\cdot}0 \times 10^{19}$ ions/cm.^{3} at 10·4°.

(*b*) An alternative interpretation is that, though sulphuric acid is incompletely dissociated, the degree of dissociation remains almost constant, so that changes in ionic concentration are, as before, much smaller than changes in mobility. This implies that ΔH_{ap} is small and, by eqn. (3), E_κ is approximately equal to E_v. Since, experimentally, $E_\kappa \simeq E_\eta$, it follows that the activation energies of viscosity and ionic migration are similar and that mobility is inversely proportional to viscosity, etc., as in (*a*). However, this hypothesis is also untenable because the autoprotolysis constant has been shown[49] to increase from $1{\cdot}7 \times 10^{-4}$ at 10·4° to $2{\cdot}9 \times 10^{-4}$ at 25°. From the relation $\Delta H_{ap} = 2{\cdot}303\ \boldsymbol{R}\ \mathrm{d}(\log K_{ap})/\mathrm{d}(1/T)$, the heat of autoprotolysis can be calculated to be 6·1 kcal. mole^{-1}.* This is not negligible. A further argument against the implication that the mobilities of the $H_3SO_4^+$ and HSO_4^- ions are viscosity-controlled is that these ions have mobilities some 50 times greater than those of other ions in the system; that is, their mobility is far greater than would be expected in a solvent of such high viscosity. Thus, at 25° the mobility of the sulphate ion in water ($\eta = 0{\cdot}894$ cP) is $8{\cdot}26 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1} which, when corrected for the viscosity of sulphuric acid ($\eta = 24{\cdot}55$ cP), gives a calculated mobility of $0{\cdot}30 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1}. This is 52 times smaller than the observed mobility of the hydrogen sulphate ion in sulphuric acid ($15{\cdot}6 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1}). It therefore appears that normal ionic migration constitutes but a small fraction of the total mobility and that the second component, the proton-switch contribution, is predominant. This is confirmed by transport measurements.[2,6]

(*c*) One is forced to conclude that the similarity in the activation energies of conduction and viscosity is fortuitous and that there is no necessary correlation in a proton-switch solvent between the activation energies of viscosity and ionic migration. This conclusion

* This was erroneously given as 2·0 kcal. mole^{-1} in ref. 49. A more recent, unpublished estimate by Dr. Gillespie gives K_{ap} (25°) $= 2{\cdot}4 \times 10^{-4}$ and $\Delta H_{ap} = 3{\cdot}8$ kcal. mole^{-1}. These variations serve to illustrate the difficulty of fixing the heat of dissociation precisely but do not affect the main line of reasoning given above.

[48] Gillespie, Hughes, and Ingold, *J.*, 1950, 2473; Gillespie, *J.*, 1950, 2516.
[49] Gillespie and Wasif, *J.*, 1953, 964.

is reinforced by the empirical observation [46] that, for a series of twelve electrolytes in sulphuric acid, there was a wide scatter of the curves when conductivity κ was plotted against concentration up to 1·5N, but that all the electrolytes fell on a common curve when the function $\kappa\eta^{\frac{1}{2}}$ was plotted against the concentration. As the concentration of ions formed by autoprotolysis of the solvent is only about 0·03N, virtually all the ions in the solution are due to the added electrolyte so that, at a given ionic concentration (n), variation in conductivity (eqn. 1) arises solely from variation in ionic mobility. It follows that in these solutions, mobility is inversely proportional to $\sqrt{\eta}$. This observation receives immediate interpretation on the present analysis for $E_\kappa = \frac{1}{2}\Delta H_{ap} + E_v$ by eqn. (3); from Table 4, E_κ is seen to have a mean value of 6·4 kcal. mole^{-1} in the range 10—25° and ΔH_{ap} was shown above to be 6·1 kcal. mole^{-1}. Hence E_v is calculated to be $3{\cdot}3_5$ kcal. mole^{-1}. From Table 4, the mean value of E_η is 6·6 kcal. mole^{-1}; thus $E_v = \frac{1}{2}E_\eta$. When the number of ions, n, is constant, then $\kappa = \kappa_0 \exp[-E_v/\boldsymbol{R}T]$ and $\eta = \eta_0 \exp[E_\eta/\boldsymbol{R}T]$. For the function $\kappa\eta^{\frac{1}{2}}$ to be constant, it is therefore necessary for $\kappa_0\eta_0^{\frac{1}{2}} \exp[(\frac{1}{2}E_\eta - E_v)/\boldsymbol{R}T]$ to be constant; *i.e.*, E_v must equal $\frac{1}{2}E_\eta$. This is the ratio just deduced. It is clear that no theoretical significance should be attached to the numerical value of the exponent $\frac{1}{2}$, as its value depends fortuitously on the values of E_κ, ΔH_{ap}, and E_η.† In particular, the semblance of a relation between viscosity and mobility should not be taken to imply a causal dependence of mobility on viscosity or to support [46] the assumption that molecular rotation rather than proton transfer is the rate-determining process in the switch mechanism. More positive evidence for this contention comes from a comparison of activation energies of conduction for sulphuric and dideuterosulphuric acids, since it is hard to imagine that the activation energy of the actual jump process would remain unaffected by substitution of the proton by a deuteron. The mechanism envisaged is a slow, rate-determining orientation of the ions and solvent molecules into positions favourable for proton jumps to occur, followed by rapid and recurring jumps in both directions across the hydrogen bridge once it is established.

(v) *Conductivity of Solid Sulphuric Acid.*—The conductivity of crystalline sulphuric acid is at least two powers of ten lower than that of the melt. The same difficulty arises here as was encountered in the preceding section in trying to apportion this decrease in conductivity between changes in the number and mobility of the ionic species present. In the case of water, it seems to be now well established [9,51] that the slight drop in conductivity on solidification is the net result of a considerable decrease in the extent of self-dissociation and a compensating increase in the mobility. This increase in mobility presumably arises from the fact that, in the ice-structure, the positioning of the molecules by hydrogen bonds ensures that the species are correctly oriented for proton-transfer to occur, so that the rate-determining prior-orientation process is no longer necessary and the mobility depends only on jump frequency.[9] However, this mechanism is only expected to hold in those cases where the proton concentration is so small that the lattice has ample time to become reoriented before the same hydrogen bridge is passed by a proton-switch chain for a second time. Although the extent of autoprotolysis in crystalline sulphuric acid is not known it is relevant that the concentration of ions formed by self-dissociation of molten sulphuric acid at 25° is nearly 10^5 times greater than the equivalent ionic concentration in water. If this difference were carried over into the solids also, it would not be surprising to find that rotation now played some part in the conduction mechanism for sulphuric acid,

† This point is emphasized by a similar calculation made for water. From values of the conductivity [50] and autoprotolysis constant [9] in the range 0—18° we calculate $E_\kappa = 10{\cdot}1$ and $\Delta H_{ap} = 13{\cdot}5$; hence $E_v = 10{\cdot}1 - \frac{1}{2}(13{\cdot}5) = 3{\cdot}35$ kcal. mole^{-1}. This calculated value agrees with the figure determined directly from the change in the sum of the mobilities of H^+ and OH^- between 0° and 18°, *viz.*, 3·45 kcal. mole^{-1}. From the viscosity of water in the same temperature range $E_\eta = 4{\cdot}44$ kcal. mole^{-1}; the ratio E_v/E_η is thus 1/1·3 for water, compared with 1/2·0 for sulphuric acid. In water, of course, both normal ionic migration and proton switches contribute appreciably to the total mobility.

[50] Kohlrausch and Heydweiller, *Wied. Annalen*, 1894, **53**, 209.
[51] Conway and Bockris, *J. Chem. Phys.*, 1958, **28**, 354.

XUM

despite the fact that is was not rate-determining in ice. Further evidence on this point would be valuable for, even in the case of ice, there remain facts which are difficult to interpret. Thus, it is believed [9] that negligible activation energy is required for the proton jump itself, the protons residing, effectively, in a conduction band of the crystal. In addition, the similar dielectric properties of ice and water encourage the belief that molecular rotation in the solid can occur almost as freely as it does in the liquid and that the heat of ionic dissociation in the two phases will be similar.[17] Nevertheless, the activation energy for conduction in ice [17] ($E_\kappa = 12{\cdot}3$ kcal. mole^{-1}) is very similar to the heat of dissociation of water ($\Delta H_{ap} = 13{\cdot}5$ kcal. mole^{-1}), and application of equation (3) then gives the activation energy of mobility $E_v = 5{\cdot}6$ kcal. mole^{-1}. This is incompatible with a theory of rate-determining proton jumps of negligible activation energy unless the heat of ionic dissociation in ice is arbitrarily taken to be 24·6 kcal. mole^{-1}.

Applying this to crystalline sulphuric acid, we have $E_\kappa = 19{\cdot}5$ kcal. mole^{-1} (Fig. 2) and the heat of autoprotolysis, taken to be the same as that of the liquid, is 6·1 kcal. mole^{-1}. Hence by eqn. (3) the activation energy of the proton-switch is 16·4 kcal. mole^{-1}. In general, the switch mechanism involves (*a*) prior orientation of the molecules and ions, (*b*) the actual proton jump, and (*c*) subsequent rotation of the solvent molecules. As the solid is known to be rigidly ordered by hydrogen bonds,[52] the prior orientation into positions favourable for proton jumps to occur, which is the rate-determining step in liquid sulphuric acid, is unnecessary. Nor can the high activation energy be ascribed to the actual proton jump itself, for this will occur more readily in the solid than in the liquid owing to the slightly closer approach of the bridged species, and even in the liquid its value cannot exceed the total activation energy of mobility (3·3 kcal. mole^{-1}). It appears that the third process, (*c*) is rate-determining and that the activation energy for this process is 16·4 kcal. mole^{-1}. This process is not rate-determining in liquid sulphuric acid because rotation occurs more readily in the melt than in the rigidly bonded crystal; the process is not rate-determining in ice because the concentration of ions is so small that there is always sufficient time for rotation before the same water molecule is involved a second time in a conduction chain. The only other consistent interpretation of the observed energies (and this appears to be far less probable) is that rotation is not rate-determining in crystalline sulphuric acid and that the jump process has but a small energy of activation. This requires that $E_\kappa \simeq \frac{1}{2}\Delta H_{ap}$, which leads to a heat of autoprotolysis in the solid of about 39 kcal. mole^{-1}; this is 6—10 times greater than the value for the liquid.

We thank the University of Nottingham for a Research Scholarship (to A. T.).

THE UNIVERSITY, NOTTINGHAM. [*Received, April 28th*, 1959.]

[52] Pascard, *Compt. rend.*, 1955, **240**, 2162; Bourre-Maladiere, *ibid.*, 1958, **246**, 1063.

701. *The Mechanism of Electrical Conduction in Fused Phosphoric and Trideuterophosphoric Acids.*

By N. N. Greenwood and A. Thompson.

The conductivity–composition curve of the system H_2O–P_2O_5 has no minimum in the region corresponding to the composition H_3PO_4, the compound being indicated instead by a discontinuous change in slope of the graph. Fused orthophosphoric acid has a high electrical conductivity ($\kappa_{40} = 7{\cdot}68 \times 10^{-2}$ ohm^{-1} cm.$^{-1}$) which decreases slowly during three weeks to an equilibrium value of $6{\cdot}52 \times 10^{-2}$ ohm^{-1} cm.$^{-1}$. Addition of potassium dihydrogen phosphate to the pure acid does not increase its conductivity but diminishes it slightly. These observations can be interpreted in terms of the rapid dissociation of phosphoric acid: $2H_3PO_4 \rightleftharpoons H_4PO_4^+ + H_2PO_4^-$, followed by a slow reaction to give an equilibrium concentration of two further ions: $2H_3PO_4 \rightleftharpoons H_3O^+ + H_3P_2O_7^-$. The ion $H_2PO_4^-$ has so high a mobility that a proton-switch conduction mechanism is implied. Consistent with this, no migration of potassium ions was detected during prolonged electrolysis of a solution of potassium dihydrogen phosphate in anhydrous phosphoric acid, all the current being carried by the dihydrogen phosphate ion. The abnormal mobility can be removed by forming the complex BF_3,H_3PO_4, in which the boron trifluoride molecules occupy positions formerly available for hydrogen bonding and proton jumps (see following paper).

The effects of deuterium substitution were determined by comparing the properties of trideuterophosphoric acid with those of phosphoric acid. As expected, deuteration raised the m. p., density and viscosity, and lowered the refractive index and conductivity. Activation energies were also derived, and the results compared with those obtained on other liquids known to conduct (*a*) by a proton-switch mechanism and (*b*) by normal ionic migration.

No systematic investigation of the conduction properties of anhydrous phosphoric acid has been published though isolated reports suggest that its electrical conductivity is abnormally high for so viscous a liquid. This paper describes the preparation and characterization of pure anhydrous orthophosphoric and trideuterophosphoric acids and the measurement of their conductivity, viscosity, and density over a temperature range of 40°. The results indicate that, even if phosphoric acid were completely dissociated into ions, the average mobility of these ions must be ten times the value for normal ionic mobilities to account for the conductivity. From the way in which the conductivity of the pure acid alters on addition of water or phosphoric oxide, it is concluded that the abnormal mobility is confined primarily to the anion $H_2PO_4^-$ (or $D_2PO_4^-$), implying an apparent migration velocity about twenty times greater than that expected for normal ionic migration. (For comparison, the mobility of the hydrogen ion in water is about six times that of other cations.) These deductions were confirmed by transport measurements and were recently published in a preliminary note.[1] The experimental results are presented in the following section and compared with data in the literature. The results are then interpreted on the basis of a proton-switch conduction mechanism in the fused acids.

Experimental and Results.

The anhydrous acids were prepared in a vacuum line by transferring the stoicheiometric amount of water or heavy water on to a known weight of phosphoric oxide which had been purified by repeated sublimation *in vacuo*.[2] Other apparatus was as described in the preceding paper.[3]

[1] Greenwood and Thompson, *Proc. Chem. Soc.*, 1959, 352.
[2] *Idem*, "Inorganic Syntheses," Vol. VI, in the press.
[3] *Idem*, preceding paper.

The m. p. of orthophosphoric acid was determined by sealing a sample into a V-tube and slowly crystallizing about four-fifths before decanting the remaining liquid into the second limb. The temperature was then raised slightly so that the crystals started to melt and this fresh liquid used to swill away the viscous film adhering to the crystals after the first decanting. The bulk of the crystals were then remelted and the whole cycle of partial crystallization, decanting, partial melting, and decanting was repeated. The m. p. rose rapidly from an initial value of about 40° for the acid as synthesized to a maximum of 42·35° (lit., 42·35°,[4,5] 42·30° [6]) and this value was not raised by further cycles. By the same technique the m. p. of trideuterophosphoric acid was determined as 46·0°, an increase of $3{\cdot}6_5$°. The only reported value for the trideutero-acid is 38·4°,[7] but this was on an admittedly impure sample and the corresponding figure for orthophosphoric acid, synthesized by the same authors for comparison, was only 40·1°.

The refractive index of orthophosphoric acid measured on an Abbé refractometer with Na_D illumination was very sensitive to traces of moisture; $n_D^{20} = 1{\cdot}4503$ (lit., 1·4510,[7] 1·45026 [8]). For trideuterophosphoric acid $n_D^{20} = 1{\cdot}4430$, which is identical with the only published value.[7]

Variation of electrical conductivity with composition at 40·0° was investigated both by adding known weights of water to phosphoric acid and its hemihydrate and also by adding weighed portions of phosphoric oxide to these compounds. Results obtained by the addition of water were reproducible, and detailed measurements in the region of 20 moles % of total P_2O_5 showed no discontinuity or inflexion at the hemihydrate, $H_3PO_4,\frac{1}{2}H_2O$. Addition of phosphoric oxide to these solutions retraced the curve in general but precise results were difficult to obtain because of the slow rate of hydrolysis of the oxide in concentrated acid at 40°. Nevertheless, there was always a definite change in slope at 25 moles % of P_2O_5 (*i.e.*, H_3PO_4) as shown in Fig. 1 which is typical of the many runs made. The lower limb could also be retraced by adding water and again a discontinuity occurred at the composition of the anhydrous acid. Phosphoric acid is therefore not characterized by a minimum in conductivity, and this property cannot be used as a criterion for purity of the acid. The absence of a minimum is also relevant to a discussion of the modes of ionization and the mechanism of conduction in orthophosphoric acid (p. 3490).

The electrical conductivity of anhydrous phosphoric acid, purified by fractional freezing in an apparatus attached directly to the conductivity cell, decreased slowly with time from an initial value characteristic of the pure freshly melted acid to a value characteristic of the slowly attained equilibrium mixture of orthophosphoric acid and higher polyphosphoric acids of the same stoicheiometry $H_4P_2O_7,H_2O$, formed by self dehydration. (This is a second reason why conductivity is not a reliable criterion of purity in this system.) In a typical experiment at 40°

TABLE 1. *Density, viscosity, and conductivity between* 25° *and* 65° *.

Temp.	d^{t}_{4} (g. cm.$^{-3}$)		η (cP)		$10^3\kappa$ (ohm^{-1} cm.$^{-1}$)		μ (ohm^{-1} cm.^{2} mole^{-1})		$\mu\eta$ (ohm^{-1} cm.^{2} cP. mole^{-1})	
	H_3PO_4	D_3PO_4	H_3PO_4	D_3PO_4	H_3PO_4	D_3PO_4	H_3PO_4	D_3PO_4	H_3PO_4	D_3PO_4
25·0°	1·8683	1·9083	177·5	231·8	4·675	2·818	2·446	1·495	434·1	346·5
30·0	1·8646	1·9042	140·8	182·4	5·589	3·378	2·937	1·791	413·6	326·9
35·0	1·8603	1·9001	112·2	147·8	6·598	3·998	3·475	2·126	389·9	314·2
40·0	1·8568	1·8959	92·69	118·7	7·680	4·632	4·053	2·467	375·8	293·0
45·0	1·8523	1·8922	76·45	95·93	8·836	5·275	4·672	2·815	357·2	270·6
50·0	1·8494	1·8888	64·01	77·44	10·13	5·940	5·366	3·176	343·5	246·0
55·0	1·8458	1·8846	54·83	64·73	11·38	6·558	6·043	3·514	331·3	227·5
60·0	1·8414	(1·8807)	46·11	55·18	12·70	7·261	6·762	3·899	304·6	215·2
65·0	1·8380	(1·8767)	39·64	46·86	14·06	(7·94)	7·495	(4·28)	297·1	(200)

* Values in parentheses were obtained by extrapolation.

on a sample sealed under vacuum into a conductivity cell which was completely immersed in the thermostat bath to eliminate the possibility of slow thermal dehydration, the initial conductivity of $7{\cdot}68 \times 10^{-2}$ ohm^{-1} cm.$^{-1}$ decreased to $6{\cdot}90 \times 10^{-2}$ in 24 hr. and to an equilibrium value of $6{\cdot}52 \times 10^{-2}$ after 21 days. The total decrease was 15% and, at equilibrium, no change

[4] Ross and Jones, *J. Amer. Chem. Soc.*, 1925, **47**, 2165; *Ind. Eng. Chem.*, 1925, **17**, 1081.
[5] Weber and King, "Inorganic Syntheses," Vol. I, 1939, p. 101.
[6] Smith and Menzies, *J. Amer. Chem. Soc.*, 1909, **31**, 1183.
[7] Pannetier and Guenebaut, *Bull. Soc. chim. France*, 1955, 636.
[8] Tutunzic, Liler, and Kosanovic, *Bull. Soc. chim. Belgrade*, 1955, **20**, 3, 363, 481.

in the conductivity could be detected (1 part in 5000) during 3 days. The time taken to reach equilibrium and the relative concentration of the various species at equilibrium depend on temperature but, as the initial (maximum) rate of change at 40° is only 0·5% per hour, it is possible, by working quickly, to get a moderately accurate set of data on the variation of the " initial " conductivity with temperature. Values so obtained are summarized in col. 6 of Table 1, and these were reproducible to within 2 parts per 1000 on independent samples of orthophosphoric acid synthesized in the vacuum line. An isolated sample was also prepared by dehydrating " AnalaR " syrupy phosphoric acid in a stream of dry air at 100° and subsequently recrystallizing the acid to maximum m. p.; the values obtained were close to those given in Table 1 and are incorporated in Table 2, which also includes the six previously reported determinations of the conductivity. There is general agreement between the values but the published figures are all higher (to varying degrees) than the present values. This discrepancy is not due to the slowly attained equilibrium with polyphosphoric acids, since this decreases rather than increases

FIG. 1. *Conductivity–composition isotherm for* H_2O–P_2O_5 *at* 40°.

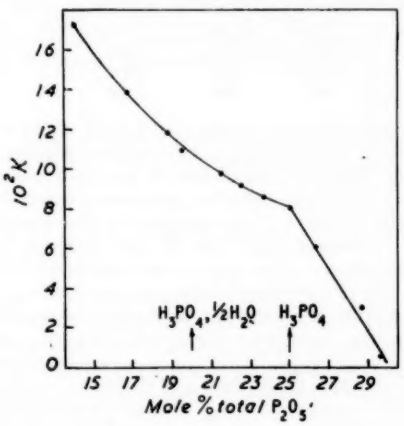
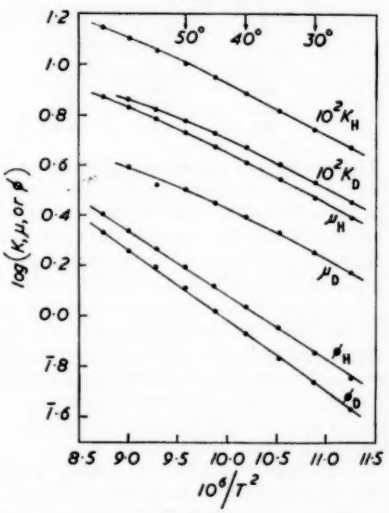


FIG. 2. *Conductivity and fluidity of* H_3PO_4 *and* D_3PO_4.



the conductivities given in Table 1. Indeed, it may well be that the literature values themselves refer to acids which had been molten for some time and that, had the measurements been made on the acids when freshly fused, they would have been even higher than those given in Table 2.

TABLE 2. *Conductivity of phosphoric acid* ($10^2\kappa$, *ohm*$^{-1}$ *cm.*$^{-1}$).

Temp.	Present work: Table 1	Present work: Dehydr. recryst. " AnalaR "	Other values
0·0°	(1·0) [a]	—	1·406 [b]
25·0	4·675	4·617	4·662—5·041,[c] 5·10,[d] 5·192,[e] 5·66 [f]
29·3	5·468	5·413	5·80 [g]
40·0	7·680	7·541	7·845—8·394 [c]

[a] Extrapolated from 25° on Fig. 2. [b] Phillips, *J.*, 1909, **95**, 59. [c] Ref. 8. [d] Topchiev, Paushkin, Vishnyakova, and Kurashov, *Doklady Akad. Nauk, S.S.S.R.*, 1951, **80**, 381. [e] Hetherington, Nichols, and Robinson, *J.*, 1955, 3141. [f] Calculated from the equivalent conductivity, $\lambda_{25} = 3{\cdot}14$, and the number of moles/l. of anhydrous H_3PO_4 (18·02) given in ref. 11. [g] By extrapolation from a value of $6{\cdot}102 \times 10^{-2}$ ohm^{-1} cm.$^{-1}$ for 98·8% H_3PO_4 given by Smith and Menzies, *J. Amer. Chem. Soc.*, 1909, **31**, 1191.

In view of the way in which conductivity varies with composition (Fig. 1), two conclusions are possible: (*a*) the acid used in the present experiments contained an excess of phosphoric oxide, or (*b*) earlier investigators used samples which contained small amounts of water. The sealed-system technique employed in this work for measuring the conductivity of maximum m. p.

acid renders contamination with phosphoric oxide unlikely. On the other hand, it is difficult to avoid the adventitious absorption of moisture when working in open systems with hygroscopic compounds such as phosphoric acid, and our own experience in preliminary experiments confirms that, even during the rapid pouring of phosphoric acid from one vessel to another, sufficient water is absorbed to increase the conductivity appreciably. We conclude that the conductivity values in Table 1 are to be preferred to the published values summarized in Table 2.

The conductivity of trideuterophosphoric acid also decreased slowly with time to an equilibrium value. Values of the initial conductivity as a function of temperature are set out in Table 1, which indicates that deuteration lowers the specific conductivity to 60% of the value for phosphoric acid itself. The temperature variation of the conductivity of the compounds could not be represented as a linear relation between log κ and $1/T$, and Fig. 2 shows that even the plot of log κ against $1/T^2$ is still slightly curved. This may reflect the changing position of equilibrium between ortho- and poly-phosphoric acids. Approximate activation energies at three temperatures are given in Table 3 and are discussed later.

TABLE 3. *Activation energies of electrical conduction and viscous flow.*

	E_κ (kcal. mole^{-1})		E_μ (kcal. mole^{-1})		E_η (kcal. mole^{-1})	
Temp.	H_3PO_4	D_3PO_4	H_3PO_4	D_3PO_4	H_3PO_4	D_3PO_4
25°	6·0	6·5	6·1	6·5	7·92	8·55
40	5·7	5·3	5·8	5·3	7·54	8·14
60	4·5	4·0	4·6	4·4	7·09	7·66

The viscosity of the two compounds at various temperatures is compared in cols. 4 and 5 of Table 1. There is a very considerable increase on deuteration (30·6% at 25°), but this diminishes to 18·2% at 65° as a result of the greater activation energy of viscous flow in the deutero-compound (see Table 3). Unlike the electrical conductivity, the viscosity showed no detectable change with time over a period of days, so that this property is less sensitive to the presence of small concentrations of polyphosphate anions. Consistent with this, the plot of log ϕ, *i.e.*, $-\log\eta$, against $1/T^2$ in Fig. 2 was linear for both compounds, the decrease in activation energy with rise in temperature being associated with the decrease in hydrogen bonding as discussed in the preceding paper.[3] The viscosity of trideuterophosphoric acid has not previously been determined, and only two references, giving widely differing values, were found for orthophosphoric acid itself. Simon and Weist [9] report $\eta_{20} = 326{\cdot}0$ cP and $\eta_{50} = 117{\cdot}37$ cP, compared with our values of 220 cP (extrapolated) and 64·01 cP., whereas Tutunzic, Liler, and Kosanovic [8] report values much nearer ours (in parentheses): $\eta_{25} = 164{\cdot}7$—$173{\cdot}3$ (177·5), $\eta_{40} = 84{\cdot}88$—$88{\cdot}95$ (92·69).

The change in density on passing from phosphoric acid to its deuterium analogue is less spectacular than the corresponding changes in conductivity and viscosity. In fact the change is insufficient to compensate for the greater molecular weight of the deutero-acid, so that there is an increase of 0·93% in the molar volume at 25°. The experimental values in Table 1 lead to the equations

$$H_3PO_4: \; d_4^t = 1{\cdot}8876 - 7{\cdot}691 \times 10^{4}t$$
$$D_3PO_4: \; d_4^t = 1{\cdot}9279 - 7{\cdot}873 \times 10^{4}t$$

The equation for phosphoric acid may be compared with the relation $1{\cdot}882$—$7{\cdot}0 \times 10^{-4}t$ derived from the data of Ross and Jones,[10] which gives $d_4^{25} = 1{\cdot}866$ (present work 1·8683). Other literature values for d_4^{25} are 1·8609 [8] and 1·8224,[10] the latter figure being particularly low. The only published density value for trideuterophosphoric acid [7] refers to acid of very low m. p.: $d_4^{20} = 1{\cdot}890$ (present work 1·9119); the value obtained by the same workers for phosphoric acid, however, $d_4^{20} = 1{\cdot}873$, agrees well with our value of 1·8729. In short, the published values for the density of the two acids either agree with or are lower than the present values.

Dissolution of potassium dihydrogen phosphate in orthophosphoric acid lowers the specific conductivity of the system indicated in Table 4. This is probably due to the removal of phosphoric acid molecules from the conduction chain when the potassium ion becomes solvated, and more detailed experiments (to be published later) using phosphoric acid hemihydrate as solvent suggest that the solvation number of the potassium is 4.

[9] Simon and Weist, *Z. anorg. Chem.*, 1952, **268**, 301.
[10] Ross and Jones, *Ind. Eng. Chem.*, 1925, **17**, 1170.
[11] Mason and Culvern, *J. Amer. Chem. Soc.*, 1949, **71**, 2387.

Electrolysis of solutions of potassium dihydrogen phosphate in phosphoric acid and of the acid itself gave hydrogen and oxygen at the electrodes in the ratio 2 : 1. Prolonged electrolysis in a transport cell similar to that described by Hammett and Lowenheim for anhydrous sulphuric acid [12] caused no measurable change in the concentration of potassium ions. For example, passage of 455 coulombs (approx. 13 mA for 10 hr.) through a 0·135m-solution of potassium

TABLE 4. *Specific conductivity of solutions at 25°.*

Molality of KH_2PO_4	0·00	0·0138	0·0370	0·0687	0·0889	0·0136	0·314
$10^3\kappa$ (ohm^{-1} $cm.^{-1}$)	4·63	4·56	4·38	4·21	4·13	3·93	3·56

dihydrogen phosphate in anhydrous phosphoric acid left the concentration of potassium ions in the anode, cathode, and central compartments identical with that of the original solution to within the precision of the analytical methods used (1%). This places an upper limit of 0·002 on the transport number of the potassium ion. In a control experiment on an aqueous solution of potassium dihydrogen phosphate, passage of 189 coulombs (approx. 13 mA for 3·5 hr.) altered the concentration from 1·96 to 1·54 g. of K^+/100 ml. in the anolyte and to 2·38 g. of K^+/100 ml. in the catholyte. These figures correspond to a transport number $t_{K^+} = 0·85$ at this concentration. This is consistent with the data of Mason and Culvern [11] who found $\lambda_0(H_2PO_4^-) = 16$; $\lambda_0(K^+)$ being taken to be 76 gives $t_{K^+} = 76/(76 + 16) = 0·83$ at infinite dilution. Potassium was determined by precipitation with sodium tetraphenylboron after adjusting the acidity to pH 3 with aqueous sodium hydroxide.

DISCUSSION

The self-dissociation of phosphoric acid can be represented by two simultaneous processes. The first is a rapidly attained autoprotolysis equilibrium:

$$2H_3PO_4 \rightleftharpoons H_4PO_4^+ + H_2PO_4^- \quad \ldots\ldots\ldots\ (1)$$

The second is a slowly attained equilibrium (2) which can be described as an ionic self-dehydration:

$$2H_3PO_4 \rightleftharpoons H_3O^+ + H_2P_2O_7^- \quad \ldots\ldots\ldots\ (2)$$

The abnormally high electrical conductivity of orthophosphoric acid cannot be explained on the basis of the normal Stokes migration of these ions even if the compound is considered to be completely ionic, since the high viscosity ($\eta_{25} = 177·5$ cP) renders any contribution from normal migration negligible. Thus, by using the equations given in the preceding paper,[3] the conductivity can be represented by the expression $\kappa = nev$, where n is now the total number of ions per ml., v their average mobility, and e is the electronic charge ($1·59 \times 10^{-19}$ coulomb). If molten orthophosphoric acid is assumed to be completely dissociated according to (1), then $n = 6·03 \times 10^{23}/V_M$ ions per ml., where V_M, the molar volume at 25°, is 52·5 ml. The mobility required to give the observed conductivity of $4·68 \times 10^{-2}$ ohm^{-1} $cm.^{-1}$ is therefore $2·55 \times 10^{-5}$ $cm.^2$ $sec.^{-1}$ $volt^{-1}$. This is ten times greater than the value of $2·5 \times 10^{-6}$ obtained on the basis of Walden's rule assuming a similar degree of ionic solvation in water and phosphoric acid and normal ionic migration. In this calculation the dihydrogen phosphate ion has a mobility [11] of $1·6 \times 10^{-4}$ $cm.^2$ $sec.^{-1}$ $volt^{-1}$ in water, and the mobility of the $P(OH)_4^+$ ion was taken to be similar to that of the ammonium or the sulphate ion, *i.e.*, about 8×10^{-4} $cm.^2$ $sec.^{-1}$ $volt^{-1}$, so that the average ionic mobility is close to 5×10^{-4} $cm.^2$ $sec.^{-1}$ $volt^{-1}$ in water ($\eta_{25} = 0·894$). This reduces to $2·5 \times 10^{-6}$ $cm.^2$ $sec.^{-1}$ $volt^{-1}$ when corrected for the viscosity of anhydrous orthophosphoric acid. The tenfold difference between this estimated ionic migration velocity and the minimum possible mobility required to reproduce the observed conductivity cannot be removed by postulating a decrease in ionic solvation and implies some abnormal conduction mechanism. If only one of the ions is abnormal then it must have an effective mobility at least twenty times that of a normal ion. This factor will, of course, be greater if the acid is not completely dissociated; for example, if molten orthophosphoric acid is 10% dissociated according to (1), then one of the ions must be moving

[12] Hammett and Lowenheim, *J. Amer. Chem. Soc.*, 1934, **56**, 2620.

some 200 times more rapidly than expected to account for the observed conductivity. The abnormal conductance is established conclusively by the transport measurements which indicate no migration of potassium ions during electrolysis of KH_2PO_4, the current being carried entirely by a proton-switch mechanism involving the ions formed by autoprotolysis of the solvent.

The shape of the conductivity–composition isotherm gives further information about the anomalously conducting species. In sulphuric acid there is a minimum in conductivity which occurs almost precisely at the composition H_2O,SO_3;[13,14] this establishes that both the HSO_4^- ion (whose concentration is increased by addition of water) and the $H_3SO_4^+$ ion (whose concentration is increased by addition of sulphur trioxide) have very similar mobilities. In the phosphoric acid system, on the other hand, there is no minimum in conductivity (Fig. 1); addition of water to the stoicheiometric acid increases its conductivity, but addition of phosphoric oxide sharply decreases it. As water is a stronger proton-acceptor than phosphoric acid, it removes protons from the $H_4PO_4^+$ ions and thus raises the concentration of dihydrogen phosphate ions according to the scheme:

$$2H_4PO_4^+ + 2H_2O \longrightarrow 2H_3O^+ + 2H_3PO_4 \quad . . . . . (3)$$

$$2H_3PO_4 \rightleftharpoons H_4PO_4^+ + H_2PO_4^- \quad . . . . . (4)$$

The overall effect of adding water to phosphoric acid is therefore summarized by equation (5):

$$H_4PO_4^+ + 2H_2O \longrightarrow 2H_3O^+ + H_2PO_4^- \quad . . . . . (5)$$

The hydroxonium ion, by analogy with its behaviour in the sulphuric acid system,[15] is unlikely to have an abnormal mobility since it is not incorporated into the three-dimensional hydrogen-bonded structure of the liquid. The increase in conductivity is therefore due to the increase in concentration of the dihydrogen phosphate ion, and this ion is thereby established as having an abnormal conductivity in anhydrous phosphoric acid. By contrast, addition of phosphoric oxide to the stoicheiometric acid reduces its conductivity. The reaction here is more complicated because of the intermediate stages involved in the solvolysis of the P_4O_{10} molecule, but the overall reaction can be written

$$P_4O_{10} + 8H_3PO_4 \longrightarrow 6H_4P_2O_7 \quad . . . . . (6)$$

The pyrophosphoric acid will then dissociate to some extent, thus increasing the concentration of $H_4PO_4^+$ ions:

$$H_4P_2O_7 + H_3PO_4 \rightleftharpoons H_4PO_4^+ + H_3P_2O_7^- \quad . . . . . (7)$$

The fact that the conductivity decreases sharply with increasing concentration of these ions indicates that neither has any appreciable abnormal mobility. The drop in conductivity is due predominantly to the decrease in concentration of the anomalously conducting dihydrogen phosphate ion which occurs (1) when molecular phosphoric acid is removed from the system by reactions (6) and (7). In its lack of anomalous mobility the $H_3P_2O_7^-$ ion resembles the $HS_2O_7^-$ ion in sulphuric acid.[16] The absence of anomalous mobility for the $P(OH)_4^+$ ion is also readily understandable since, like the NH_4^+ ion, it is symmetrical and has no dipole moment to confer a preferred orientation in the applied electric field. Thus, whether or not the ion is involved in proton switches across hydrogen bonds, it will not contribute to the conductivity since these transfers will occur randomly rather than preferentially in the direction of the field.

The slow decrease in the conductivity of freshly melted phosphoric acid to an equilibrium value receives explanation in terms of eqn. (2) and the known sluggishness of interconversion of the polyphosphoric acids, for removal of molecular phosphoric acid by (2) shifts equilibrium (1) so as to reduce the concentration of the anomalously conducting

[13] Kunzler and Giauque, *J. Amer. Chem. Soc.*, 1952, **74**, 804.
[14] Gillespie, Oubridge, and Solomons, *J.*, 1957, 1804.
[15] Gillespie and Wasif, *J.*, 1953, 221.
[16] *Idem*, *ibid.*, p. 964.

dihydrogen phosphate ion. The Kohlrausch mobility of the other three ions is negligible as shown above. The build-up of new species in the melt was confirmed cryoscopically, the m. p. of the acid decreasing steadily by several degrees over a period of days as reaction (2) proceeded. That the process was reversible was demonstrated by crystallizing orthophosphoric acid very slowly from an equilibrium melt. The m. p. was raised to the initial value and the conductivity on remelting had returned to its initial high value; thereafter both m. p. and conductivity fell as before to an equilibrium value, the whole cycle being repeatable indefinitely. There is abundant independent evidence of the presence of the pyrophosphate grouping in anhydrous phosphoric acid,[17,18] and several attempts have been made to determine its concentration quantitatively. Early results from chemical analysis indicated about 6 moles % of polyphosphates,[19] and radio-phosphorus exchange followed by elution from an anion-exchange resin indicated 4 moles % of pyrophosphate.[20] More recent work, using cold hydrolysis and paper chromatography, suggests that stoicheiometric orthophosphoric acid contains 6·3 moles % each of pyrophosphoric acid and "free water,"[21] whereas results obtained by gradient elution supplemented by ascending one- and two-dimensional paper chromatography suggest that the composition of the melt is 86·3 moles % of H_3PO_4, 6·8 moles % each of $H_4P_2O_7$ and H_2O, and 0·03 mole % of $H_5P_3O_{10}$.[22] These figures are entirely consistent with the 15% decrease in the conductivity, which leads to an approximate figure of 7·5 moles % for the concentration of pyrophosphate. The argument is as follows. Let the concentration of dihydrogen phosphate ions in the freshly melted acid be α moles %; then by (1) there will be α moles % of $H_4PO_4^+$ and $(100 - 2\alpha)$ moles % of undissociated H_3PO_4. At equilibrium, let there be β moles % each of $H_4PO_4^+$ and $H_2PO_4^-$ and x moles % each of H_3O^+ and $H_3P_2O_7^-$; the concentration of undissociated H_3PO_4 is then $(100 - 2\beta - 2x)$ moles %. The equilibrium constant K_1 should be independent of the presence of other equilibria, hence

$$K_1 = \frac{[H_4PO_4^+][H_2PO_4^-]}{[H_3PO_4]^2} = \frac{\alpha^2}{(100 - 2\alpha)^2} = \frac{\beta^2}{(100 - 2\beta - 2x)^2} \quad . \quad (8)$$

Taking square roots and cross multiplying, we have $\alpha(100 - 2x) = 100\beta$, so that $2x = 100(1 - \beta/\alpha)$. If the reduction in conductivity is ascribed solely to the decrease in concentration of the dihydrogen phosphate ion, then $\beta/\alpha = 0{\cdot}85$, and substitution of this above gives $x = 7{\cdot}5$ moles %.

It should be possible to detect the gradual formation of 7 moles % of a new species cryoscopically, and this was qualitatively indicated by the steady decrease in the freezing point of anhydrous phosphoric acid when it was kept molten. A quantitative determination of the concentration of pyrophosphate ions requires a knowledge of the cryoscopic constant, k_t, of phosphoric acid. This can be calculated from the heat of fusion, ΔH_t, by means of the relation $k_t = RT_0^2/(m_1\Delta H_t)$, where T_0 is the initial m. p. of pure phosphoric acid, 315·5°K, and m_1 is the number of moles of phosphoric acid per kg., *i.e.*, 10·20. The classical value for the heat of fusion [23] is 2·52 kcal. mole^{-1}, but the more recent value [18] of 3·10 kcal. mole^{-1} is preferred. Hence $k_t = 6{\cdot}26$ deg. mole^{-1} kg. The molal concentration, m_2, of pyrophosphate ions is then $\Delta T/2k_t$, where ΔT is the lowering of the freezing point and the factor 2 arises because the formation of each ion of $H_3P_2O_7^-$ is accompanied by the formation of an H_3O^+ ion which is also cryoscopically active. The equilibrium freezing point of stoicheiometric phosphoric acid was approached several weeks after the initial melting of a given sample and was about 34·6°; ΔT is thus $7{\cdot}7_5$° and $m_2 = 0{\cdot}62$ mole kg.$^{-1}$. Otherwise expressed, each kg. of solution contains 60 g. of $H_3PO_7^-$, 12 g. of

[17] Simon and Schulze, *Z. anorg. Chem.*, 1939, **242**, 313.
[18] Egan and Wakefield, *J. Phys. Chem.*, 1957, **61**, 1500.
[19] Bell, *Ind. Eng. Chem.*, 1948, **40**, 1464.
[20] Higgins and Baldwin, *Analyt. Chem.*, 1955, **27**, 1780.
[21] Huhti and Gartaganis, *Canad. J. Chem.*, 1956, **34**, 785.
[22] Jameson, *J.*, 1959, 752.
[23] Thomsen, *Ber.*, 1874, **7**, 994; N.B.S. Circular 500.

XUM

H_3O^+, and 928 g. (9·47 moles) of the monomeric phosphoric species H_3PO_4, $H_4PO_4^+$, and $H_2PO_4^-$, so that the concentration of pyrophosphate is 5·8 moles %. This is in good agreement with the values of 6·3 and 6·8 moles % obtained by chromatography and 7·5 moles % deduced from the slow decease in electrical conductivity, the differences being ascribable to deviations from ideality, to slight changes in the proton-switch mobility in the presence of the new ions, and to the inherent difficulties of chemical and chromatographic analysis for pyrophosphate in the presence of excess of orthophosphate.

The precise extent of the autoprotolysis (1) cannot be determined from the present results, but an indication of the degree of self-dissociation comes from the absolute value of the specific conductivity if a reasonable value for the proton-switch mobility can be arrived at. In water at 25°, the H_3O^+ ion has a total mobility of $36·3 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1}; some of this will be contributed by the normal ionic migration velocity of the ion, and if this is taken to be the same as that of the potassium or the ammonium ion, *viz.*, $7·6 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1}, then the proton-switch mobility is approximately $28·7 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1}. Similarly, the total mobility of the OH^- ion, $20·6 \times 10^{-4}$ cm.^{2} sec.^{1} volt^{-1}, can be considered as comprising a normal component, say, $6·2 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1} by comparison with the fluoride ion, and a proton-switch component of approximately $14·4 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1}. In sulphuric acid, because of the higher viscosity, the contribution from normal migration to the total mobility of the $H_3SO_4^+$ and HSO_4^- ions is only about 3%,[24] and as the observed mobility of the HSO_4^- ion [15] is $15·6 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1}, the proton-switch mobility in this medium is approximately $15·1 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1}. This is very similar to the anomalous part of the mobility of the hydroxyl ion but somewhat less than that of the hydroxonium ion in water. It therefore seems reasonable to assume a proton-switch mobility in phosphoric acid of the order of 20×10^{-4} cm.^{2} sec.$^{-1}$ volt^{-1}. Substitution of this and the initial conductivity into the expression $\kappa = nev$ gives $1·47 \times 10^{20}$ as the number of $H_2PO_4^-$ ions per ml. As there is the same concentration of $H_4PO_4^+$ ions, the total number of ions/ml. in the freshly melted acid is $2·94 \times 10^{20}$. Complete dissociation according to (1) would afford $6·03 \times 10^{23}/52·5$ ions per ml. as shown above. Hence the degree of dissociation is 2·56%, and the initial concentration of each of the ionic species 0·13 m. This leads to an autoprotolysis constant ($K_{ap} = [H_4PO_4^+][H_2PO_4^-]$) of $1·7 \times 10^{-2}$ mole^2 kg.$^{-2}$ at 25°, a figure which can be compared with $K_{ap}(H_2SO_4) = 2·9 \times 10^{-4}$, and $K_{ap}(H_2O) = 1·01 \times 10^{-14}$ mole^2 kg.$^{-2}$. In short, if the proton-switch mobility in anhydrous phosphoric acid is similar to that in sulphuric acid and in water, then the initial concentration of ions in phosphoric acid is about 8 times higher than in sulphuric acid and is greater than the ionic concentration in pure water by a factor of $1·3 \times 10^6$.

The general conduction characteristics of trideuterophosphoric acid are similar to those of orthophosphoric acid, and specific differences have already been mentioned under Experimental and Results. Unlike sulphuric acid, in which deuterium substitution surprisingly leaves the activation energies of conduction and viscous flow virtually unchanged,[3] deuteration of phosphoric acid has a marked influence, particularly on the viscosity. There is insufficient information to deduce the rate-determining step of the proton-switch process from these changes, or to apportion the decrease in conductivity on deuteration between the decrease in degree of self-dissociation and the decrease in switch mobility. The effect of the slow equilibrium (2) is also a complicating factor in the analysis. However, it is clear that deuterium substitution diminishes the reduced conductivity ($\mu\eta$ in Table 1) by 20% at 25° and 30% at 60° implying, as expected for a proton-switch conductor, that the conductivity is not viscosity-controlled. This contrasts with the behaviour of the boron trifluoride adducts of these acids which are discussed in the following paper; in these, conduction occurs by normal ionic migration, and the reduced conductivity is independent of temperature and is insensitive to deuterium substitution.

THE UNIVERSITY, NOTTINGHAM. [*Received, April 28th,* 1959.]

[24] Gillespie and Wasif, *J.*, 1953, 209.

702. *Addition Compounds of Boron Trifluoride with Orthophosphoric and Trideuterophosphoric Acids.*

By N. N. Greenwood and A. Thompson.

Fused orthophosphoric acid absorbs 1·084 moles of boron trifluoride at room temperature with considerable evolution of heat. Trideuterophosphoric acid behaves similarly. In both systems, addition of boron trifluoride was accompanied by a marked reduction in viscosity and electrical conductivity. These effects, which are the reverse of those normally observed when boron trifluoride is added to a ligand, are due to a progressive reduction in the extent of hydrogen bonding and to the replacement of a proton-switch conduction mechanism in the pure acids by one involving normal ionic migration in the molten complexes. The 1 : 1 compounds BF_3,H_3PO_4 and BF_3,D_3PO_4 are but poorly defined and solidify to glasses at about −100°. Nevertheless, it was possible to show that their properties were not markedly influenced by deuterium substitution and that the compounds were almost completely dissociated into ions.

The experiments now reported were undertaken to discover whether the considerable influence which deuterium substitution has on the properties of phosphoric acid [1] persisted when the system was modified so as to render electrical conduction by proton jumps unlikely. The method chosen was to study the 1 : 1 addition compounds of orthophosphoric acid and trideuterophosphoric acid with boron trifluoride. Unfortunately, the physical properties of these complexes are difficult to determine accurately because the compounds cannot be purified either by distillation or by fractional crystallization; they decompose when distilled at atmospheric pressure, immediately lose some boron trifluoride when evacuated at room temperature, and solidify to a glassy mass when cooled to −100°. The data obtained are therefore necessarily less accurate than those obtained on more readily purified compounds, and a study of the influence of deuterium substitution depends for its reliability on the prior purification of the components and their accurate stoicheiometry on reaction. For this reason the properties of boron trifluoride–orthophosphoric acid which have already appeared in the literature [2] were redetermined under conditions identical with those used for the trideutero-compound, the two complexes having been synthesized to within one part in 10,000 parts by weight. The results, besides showing that complex formation removes the marked difference in properties between phosphoric and trideuterophosphoric acid themselves, are also relevant to a discussion of the catalytic properties of these compounds.

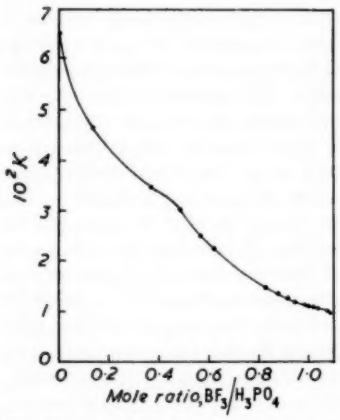
Boron trifluoride–phosphoric acid is one of the most powerful catalysts known for alkylation and polymerization of olefins, and its catalytic properties have been extensively studied by Topchiev and his collaborators during the past decade.[3] In an attempt to correlate this reactivity with the physical properties of the catalyst, these workers observed that, for a given batch of catalyst, the decrease in activity in successive runs was paralleled by a decrease in the electrical conductivity of the catalyst and that specific conductivity was a useful criterion for establishing when the catalyst was spent.[4] On the other hand, when several different catalysts were compared, there appeared to be no relation between conductivity and catalytic activity.[5] In particular, it was pointed out that, whereas the conductivity of phosphoric acid decreased substantially on addition of boron trifluoride,

[1] Greenwood and Thompson, preceding paper.
[2] Topchiev and Paushkin, *Neftyanoe Khoz.*, 1947, **25**, No. 6, 54.
[3] *Idem*, "The Use of Boron Trifluoride and its Compounds as Catalysts in Alkylation and Polymerization Reactions," Moscow, Izdatel. Akad. Nauk, S.S.S.R., 1955, 53 pp.
[4] Topchiev, Paushkin, Vishnyakova, and Kurashov, *Doklady Akad. Nauk, S.S.S.R.*, 1951, **80**, 611.
[5] *Idem, ibid.*, p. 381.

the catalytic activity of the system was considerably enhanced. From this it was concluded that catalytic activity was not related to the concentration of ions in the catalyst.[4,5] The apparent paradox in these two sets of observations arises from the misconception that electrical conductivity and ionic concentration are necessarily proportional to each other. However, conductivity depends not only on the number of ions but also on their mobility, which in turn normally depends to some extent on viscosity, so that no parallelism is to be expected between ionic concentration and specific conductivity in media of different viscosity. The situation is even more complex in the phosphoric acid system, since conduction in the pure acid occurs by a proton-switch mechanism [1] whereas, as will be shown below, the complex conducts by normal ionic migration. In addition, of course, there may well be specific chemical differences which obscure any simple correlation between conductivity and catalytic activity in the different systems.

Experimental and Results

Boron trifluoride–orthophosphoric acid and boron trifluoride–trideuterophosphoric acid were synthesized on the 30 g. scale by direct absorption of boron trifluoride in the anhydrous acids until the theoretical increase in weight was obtained (±0·2 mg.). The complexes could not be crystallized but set to transparent glassy solids at about −100° (lit.[3] *ca.* −105°). As the compounds could not be evacuated without loss of boron trifluoride, they were poured directly into the conductivity cell and dilatometer and forced by pressure of dry nitrogen through a sinter into the viscometer. In other respects techniques were as previously described.[6] The properties were reproducible and the conductivity, in contrast to that of phosphoric acid,[1] showed no variation with time.



Specific conductivity for the system BF_3–H_3PO_4 *at* 40°.

Table 1 summarizes data on the density, viscosity, and conductivity of the two complexes between 25° and 40°. Densities can be represented by the equations

$$d_4^t\,(BF_3,H_3PO_4) = 1{\cdot}9087 - 1{\cdot}02 \times 10^{-3}t$$
$$d_4^t\,(BF_3,D_3PO_4) = 1{\cdot}9370 - 1{\cdot}25 \times 10^{-3}t$$

The calculated value of the density of the complex BF_3,H_3PO_4 at 20° is 1·8883, compared with values of 1·932[2] and 1·930[7] obtained on saturated solutions of boron trifluoride in phosphoric acid.

The viscosity of the phosphoric acid complex at 20° is given in the literature as 46·7 cp;[1] this is rather lower than the value of 54·1 cp obtained from a logarithmic extrapolation of the values in Table 1. The published conductivity,[4] $\kappa_{25} = 7{\cdot}227 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$, is also lower than the value of $8{\cdot}23 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$ obtained in this work. As both the viscosity and the conductivity of the parent acid are much higher than those of the complex, these figures suggest that the earlier data were obtained on samples containing more boron trifluoride than corresponded to the 1 : 1 complex. To test this, the conductivity of a sample of phosphoric acid was investigated at 40° as boron trifluoride was progressively added (see ref. 8 for design of cell). The results, shown graphically in the Figure, indicate that successive additions of boron trifluoride continuously lowered the conductivity of the system and that the 1 : 1 ratio was not characterized by any inflexion or discontinuity. Furthermore, boron trifluoride could be added up to a mole ratio of 1·084 at which point the conductivity was 14% lower than that of the 1 : 1 compound. A temperature run on the saturated solution led to a value of $\kappa_{25} = 7{\cdot}16 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$, in close agreement with the value of 7·227 ohm^{-1} cm.$^{-1}$ given by Topchiev *et al.*[4] It can be assumed that their density and viscosity data also refer to a saturated solution rather than the 1 : 1 complex.

[6] Greenwood and Thompson, *J.*, 1959, 3474.
[7] Topchiev, Paushkin, and Machus, *Doklady Akad. Nauk, S.S.S.R.*, 1947, **58**, 815.
[8] Greenwood, Martin, and Emeléus, *J.*, 1951, 1328.

TABLE 1. *Density, viscosity, and conductivity of* BF_3,H_3PO_4 *and* BF_3,D_3PO_4.

Temp.	d_4^t (g. cm.$^{-3}$)		η (cP)		$10^3\kappa$ (ohm^{-1} cm.$^{-1}$)		2μ (ohm^{-1} cm.^{2} mole^{-1})		$2\mu\eta$ (ohm^{-1} cm.^{2} cP mole^{-1})	
	H	D	H	D	H	D	H	D	H	D
25·0°	1·8831	1·9058	46·16	48·51	8·23	8·20	1·449	1·454	66·9	70·5
30·0	1·8777	1·8990	39·27	41·66	9·29	9·25	1·641	1·646	64·4	68·5
35·0	1·8734	1·8933	34·36	35·85	10·41	10·37	1·848	1·853	63·4	66·4
40·0	1·8681	1·8870	30·35	31·11	11·85	11·50	2·105	2·062	63·9	64·3

Conductivity measurements on the stoicheiometric compounds were extended to lower temperatures, and Table 2 presents the results. The similarity in values between the two complexes persists down to −50°.

TABLE 2. *Electrical conductivity* ($10^3\kappa$ ohm^{-1} cm.$^{-1}$) *below room temperature.*

Temp.	−50°	−40°	−30°	−20°	−10°	−5°	0°	+5°	10°	15°	20°
BF_3,H_3PO_4 ...	0·259	0·551	1·046	1·745	2·718	3·288	3·951	4·676	5·46	6·32	7·24
BF_3,D_3PO_4 ...	0·238	0·505	0·995	1·690	2·634	3·232	3·888	4·607	5·38	6·26	7·19

DISCUSSION

The molar volumes of the 1 : 1 complexes at 25° are 88·06 and 88·59 ml., the deuterium compound being the larger by 0·60% (cf. the phosphoric acids, 0·98% [1]). The diminished effect of deuterium substitution in the complexes is consistent [6] with a decrease in the number of hydrogen bonds when boron trifluoride is added to phosphoric acid but, in view of the difficulty of handling these compounds, it would be unwise to emphasise unduly these slight changes in molar volume.

A more direct indication of the reduction in the extent of hydrogen bonding comes from the viscosity. The data in Table 1 for the viscosity of the complexes at 25° (46·16 and 48·51 cP), when compared with those for the phosphoric acids themselves [1] (177·5 and 231·8 cP), show that the complexes are appreciably more mobile and that the influence of deuterium substitution in increasing the viscosity has been reduced from 30·6% to 5·1%. Furthermore, the activation energy of viscous flow, E_η, is also less in the complexes: 5·33 and 5·45 kcal. mole^{-1} for BF_3,H_3PO_4 and BF_3,D_3PO_4 as compared with 8·03 and 8·51 kcal. mole^{-1}, respectively, for the parent acids. The complexes are therefore unique among the addition compounds of boron trifluoride since both viscosity and activation energy of viscous flow are normally greater for the complexes than for the ligands from which they are formed. Even the monohydrate and dihydrate of boron trifluoride have a higher viscosity than water itself, though the activation energies for the monohydrate and monodeuterate are less than for water and heavy water [9,10] where hydrogen bonding again leads to abnormally high values for the ligand.

The electrical conductivity also reflects the profound structural changes which occur when boron trifluoride is added to the phosphoric acids. The acids themselves have an abnormally large conductivity because of a proton-switch mechanism which involves the $H_2PO_4^-$ and $D_2PO_4^-$ ions.[1] There is no reason to suppose, however, that conduction in the complexes occurs by other than normal ionic transport. Consistently with this, the conductivity (Table 1) shows little change when deuterium replaces hydrogen, in contrast to the behaviour of phosphoric and sulphuric acids whose conductivity is appreciably lowered by deuteration.[1,6] Though part of this decrease, at least with sulphuric acid, is due to a change in the degree of ionic self-dissociation,[11] part is also due to the sensitivity of the conduction mechanism to replacement of protons by deuterons in the hydrogen bridges. By contrast, the slight change in ionic mass occasioned by deuteration of the complex will have little effect on the ionic migration velocity.[8,10]

[9] Greenwood and Martin, *J.*, 1951, 1915.
[10] Greenwood, *J. Inorg. Nuclear Chem.*, 1958, **5**, 224, 229.
[11] Flowers, Gillespie, Oubridge, and Solomons, *J.*, 1958, 667.

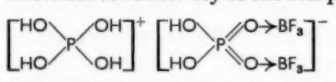
XUM

Logarithmic plots of the specific conductivity and molar conductivity ($\mu = \kappa V_M$) against the reciprocal of the absolute temperature are linear between 5° and 40° and lead to the following activation energies (in kcal. mole^{-1}):

BF_3,H_3PO_4	:	E_κ 4·24,	E_μ 4·34;	cf. E_η 5·33
BF_3,D_3PO_4	:	E_κ 4·24,	E_μ 4·35;	cf. E_η 5·45

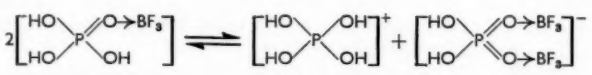
At lower temperatures the values rise steadily until, at −50°, E_κ is 7·65 kcal. mole^{-1}. It is seen that deuterium substitution has no significant effect on the activation energies of conduction. This is entirely consistent with conduction by means of ionic migration but does not, by itself, unambiguously establish this mechanism since the activation energy of conduction by the proton-switch mechanism is also apparently insensitive to deuterium substitution.[1,6]

Boron trifluoride–phosphoric acid has been formulated [12] as $[H^+]_3[PO_4,BF_3]^{3-}$, but this cannot be reconciled with the compound's monomeric molecular weight in molten phenol.[2] The simplest structure which is consistent with this fact and also with the high electrical conductivity of the compound is inset. Moreover, this structure provides a simple



interpretation of the stoicheiometry of the compound since it implies donor–acceptor bonding by both "phosphoryl" oxygen atoms but by none of the hydroxylic oxygen atoms. A compound containing half this amount of boron trifluoride is also conceivable and its formation may be indicated by the slight irregularity in the conductivity–composition graph at the mole ratio 0·5. By contrast, it is not clear why the phosphate ion in a compound such as $[H^+]_3[PO_4,BF_3]^{3-}$ should absorb only one mol. of boron trifluoride, especially as the compounds $[Na^+]_3[PO_4,3BF_3]^{3-}$ and $[K^+]_3[PO_4,3BF_3]^{3-}$ are known.[13] The structure now proposed, $[P(OH)_4]^+$ $[(OH)_2P(OBF_3)_2]^-$, also indicates clearly why addition of boron trifluoride to phosphoric acid represses electrical conduction by the proton-switch mechanism since, first, the boron atoms occupy co-ordination positions on the phosphoryl oxygen atoms formerly available to protons in hydrogen bridges, and secondly, donor–acceptor bond formation so reduces the electron density around the oxygen atoms that there is little chance of forming hydrogen bridges of sufficient strength at the remaining oxygen co-ordination position for proton transfer to occur.

On the basis of this structure and the simple theory of ionic mobilities in molten complexes [14] it is possible to calculate approximately the extent to which the complex exists in the ionic form:



As two moles of complex are required to produce a uni-univalent electrolyte, the appropriate measure of the percentage degree of ionic dissociation, α, is $2\mu\eta$ and this quantity is tabulated in the last column of Table 1. The values obtained lie in the range 60—70%. In view of approximate nature of the calculation and the assumption necessarily made about the absolute magnitude of the ionic mobilities, these figures may well indicate that the complexes are virtually completely dissociated into ions.

THE UNIVERSITY, NOTTINGHAM.

[*Received, April 28th,* 1959.]

[12] Paushkin, *Zhur. priklad. Khim.*, 1948, **21**, 1199.
[13] Baumgarten and Hennig, *Ber.*, 1939, **72**, 1743.
[14] Greenwood and Martin, *J.*, 1953, 1427.

703. *Vapour-phase Photochemical Chlorination and Bromination of 2,2,4,4-Tetramethylpentane.*

By J. D. Backhurst.

2,2,4,4-Tetramethylpentane has been chlorinated and brominated in illuminated reactions at 135°. 1-Halogeno- and 3-halogeno-2,2,4,4-tetramethylpentane were found and there was no evidence for rearrangement of the carbon skeleton. Hydrolysis, with 80% aqueous ethyl alcohol, was used for the analysis of products, and this reaction was greatly accelerated by the addition of silver nitrate.

The direct bromination of 2,2,4,4-tetramethylpentane was studied by Kharasch, Liu, and Nudenberg,[1] who reported that only a rearranged product, 2-bromo-2,3,4,4-tetramethylpentane, had been found. The free-radical mechanism postulated involves the migration of a methyl radical at an intermediate stage, and the evidence for this has been questioned by Walling,[2] who suspects a polar rearrangement of the expected, unrearranged, 3-bromo-2,2,4,4-tetramethylpentane. Liquid-phase chlorination of the hydrocarbon has been investigated by Davies,[3] who found only the expected substitution products, *viz.*, 1-chloro- and 3-chloro-2,2,4,4-tetramethylpentane.

Analyses of the products by Kharasch *et al.* and by Davies were markedly different. The former employed (*a*) hydrolysis with 75% aqueous ethyl alcohol and an excess of silver nitrate, (*b*) acetolysis in the presence of silver nitrate, and (*c*) reaction with silver 3,5-dinitrobenzoate to give 2,3,4,4-tetramethylpent-1-ene. Davies employed a kinetically controlled hydrolysis with 80% aqueous ethyl alcohol. The methods used by Kharasch *et al.* do not rule out the possibility that the bromo-compound formed during the reaction was the expected substitution product which subsequently underwent a silver-ion catalysed, carbonium-ion rearrangement.

I have re-investigated the bromination of the hydrocarbon in the vapour-phase, with illumination by mercury arcs, and also studied the chlorination under similar conditions. In both cases, the expected, unrearranged, substitution products were formed, *i.e.*, primary and secondary halides. The isomeric halides could not be separated by careful fractional distillation, and analysis was performed by a study of the kinetically-controlled hydrolysis with 80% aqueous ethyl alcohol. The structure of each component was deduced from the first-order rate coefficients. The structure, *i.e.*, primary, secondary, or tertiary, of an unknown alkyl halide can be deduced from this rate coefficient by comparison with that of a known compound, *e.g.*, t-butyl halide or isopropyl halide, under the same conditions.

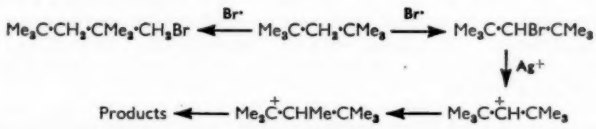
With chlorination, no reaction took place at 25° during the first 47 hours and it was concluded that no tertiary, *i.e.*, rearranged, chloro-compound was present. At 100·4° a steady reaction took place during the first 100 hours but after this time the rate decreased considerably. First-order rate coefficients for these two reactions were $7{\cdot}68 \times 10^{-6}$ sec.$^{-1}$ and $1{\cdot}91 \times 10^{-8}$ sec.$^{-1}$. These values are in agreement with those obtained for the hydrolysis of the material from the liquid-phase chlorination of the hydrocarbon.[3] From the hydrolysis data it was calculated that 20% of the product was the secondary chloride, as would be expected from Hass, McBee, and Weber's " Rules for Chlorination."[4]

With the monobrominated product, hydrolyses were carried out at 25·0° and 73·05°. At 25° no reaction took place during the first five hours and it was concluded that no tertiary, *i.e.*, rearranged, bromo-compound was present. At 73·05° a steady reaction took place during the first 25 hours but after this time the reaction rate decreased considerably. First-order rate coefficients for these two reactions were $2{\cdot}93 \times 10^{-5}$ sec.$^{-1}$, and $3{\cdot}36 \times 10^{-8}$

[1] Kharasch, Liu, and Nudenberg, *J. Org. Chem.*, 1954, **19**, 1150; 1955, **20**, 680.
[2] Walling, " Free Radicals in Solution," John Wiley and Sons, Inc., New York, 1957, p. 373.
[3] Davies, Ph.D. Thesis, University of Wales, 1950.
[4] Hass, McBee, and Weber, *Ind. Eng. Chem.*, 1935, **27**, 1190; 1936, **28**, 333.

sec.$^{-1}$. Calculation showed that 82% of the product was secondary bromide. A hydrolysis carried out at room temperature, 21°, in the presence of an excess of silver nitrate proceeded rapidly, whereas in the absence of silver nitrate there was no reaction.

This indicates that when the unrearranged substitution products react in the presence of silver ions a carbonium-ion reaction takes place, leading to rearrangement. The over-all reaction may be represented as follows:—



The relative proportions of secondary halide produced during the reaction, *i.e.*, 20% and 82% respectively for chlorination and bromination, were of the order expected after taking into consideration the variation of activation energies for halogen attack on primary and secondary C–H bonds. In the case of chlorination the activation energy for attack on a secondary C–H bond is approximately 650 cal. mole^{-1} lower than for the primary bond, whilst for bromination this decrease is greater and hence bromination is more specific. Halogenation of n-butane and isobutane in the gas phase has been studied by Anson, Fredricks, and Tedder [5] and the above values for the secondary halides agree with their " Relative Selection " values of chlorine and bromine for primary and secondary hydrogen atoms.

Experimental

The apparatus and technique for chlorination have been described previously.[6] For bromination, a vaporizer for the bromine, similar to that used for the hydrocarbon, replaced the apparatus used for drying and metering the chlorine. All experiments were carried out at atmospheric pressure.

Materials.—Chlorine was the middle fraction from a commercial cylinder and was dried before use. " AnalaR " bromine was used without further treatment.

2,2,4,4-*Tetramethylpentane.* Howard's method [7] was employed for the preparation of this hydrocarbon, b. p. 122·2—122·7°/752—768 mm., n_D^{25} 1·4450 (Found: C, 84·3; H, 16·0. Calc. for C_9H_{20}: C, 84·3; H, 15·7%), yield 44%.

Chlorination.—The hydrocarbon (144 ml.) was vaporized during 40 min., the rate of flow of the chlorine was 5·0 litres per hr. to give a hydrocarbon : chlorine ratio of 5·9, the reaction temperature was 135°, and the contact time about 22 sec. Fractional distillation under reduced pressure yielded unchanged hydrocarbon and 10 g. (yield 45%) of monochlorinated material, b. p. 38·5–39·0°/3·5 mm., n_D^{25} 1·4401. A similar experiment, with 500 ml. of the hydrocarbon, a contact time of about 34 sec. at 135°, and a hydrocarbon : chlorine ratio of 4·1, yielded 55·2 g. (yield 50%) of the monochlorinated material, b. p. 45·9°/5 mm., n_D^{25} 1·4402.

Hydrolyses.—Standard techniques were employed and the hydrogen chloride liberated was estimated by titration with standard sodium ethoxide solution, lacmoid being used as an indicator.

At 25° no reaction took place during the first 47 hr. *Reaction at* 100·4°. 0·7065 g. of the product was made up to 100 ml. with 80% aqueous ethyl alcohol [8] and 5·35 ml. samples were sealed up, immersed in a thermostat, and removed at suitable time intervals, and the hydrogen chloride content was determined:

Time (hr.)	0·0	1·0	3·0	5·0	8·42	21·5	25·0
Titre (ml.)	0·05	0·17	0·40	0·63	0·96	2·11	2·33
Time (hr.)	30·0	51·0	98·0	165·0	343·0	511·0	607·0
Titre (ml.)	2·60	3·38	4·04	4·15	4·34	4·42	4·65

[5] Anson, Fredricks, and Tedder, *J.*, 1959, 918.
[6] Backhurst, Hughes, and Ingold, *J.*, 1959, 2742.
[7] Howard, *J. Res. Nat. Bur. Stand.*, 1940, **24**, 679.
[8] Grunwald and Winstein, *J. Amer. Chem. Soc.*, 1948, **70**, 852.

A plot of the titre against time showed that two reactions were proceeding, one of which was essentially complete after 100 hr.

Under the reaction conditions the reaction would be of first order, and rate coefficients were calculated accordingly. From the weight of chloride taken and the known concentration of the ethoxide solution, the titre after complete reaction, *i.e.*, infinity titre, was calculated to be 21·94 ml.; from the experimental data the titre of ethoxide solution equivalent to the " fast " (more readily hydrolysed) chloride was calculated to be 4·49 ml.; hence the monochlorinated material contained 20·5% of " fast " chloride. First-order rate coefficients for the " fast " chloride were calculated from the usual rate equation and also by Guggenheim's method.[9] A graphical method was used to calculate the rate coefficient for the " slow " (less readily hydrolysed) chloride.

Bromination.—The hydrocarbon (155 ml.) was vaporized and treated with bromine (29·3 g.) during 80 min.; the reaction temperature was 135°, the contact time 30 sec., and the hydrocarbon : bromine ratio 6·6. Unchanged hydrocarbon was recovered by fractional distillation and a second experiment carried out with 112 ml. of the hydrocarbon and 23·5 g. of bromine, contact time 26 sec., reaction temperature 135°, and hydrocarbon : bromine ratio 6·0. The unchanged hydrocarbon was recovered and the brominated product from both reactions fractionally distilled to yield 31·8 g. (yield 47%) of monobrominated material, b. p. 56·1—56·5°/5 mm., n_D^{25} 1·4692 (Found: C, 51·5; H, 9·1; Br, 39·8. Calc. for $C_9H_{19}Br$: C, 52·2; H, 9·2; Br, 38·6%); the residue from the distillation yielded white crystals which analysed correctly for a dibromide (Found: C, 37·3; H, 6·2; Br, 54·8. Calc. for $C_9H_{18}Br_2$: C, 37·8; H, 6·4; Br, 55·8%). Other experiments gave similar results.

Hydrolyses.—At 25° no reaction occurred during the first 5 hr. *Reaction at* 73·05°. 0·8347 g. of the product was made up to 100 ml. with 80% aqueous ethyl alcohol and 5·35 ml. samples treated as above:

Time (hr.)	0·0	0·5	1·0	1·5	2·5	3·0	4·0	6·0	8·0
Titre (ml.)	0·20	1·02	1·84	2·54	3·88	4·53	5·75	7·79	9·53
Time (hr.)	11·25	22·0	29·0	54·7	94·1	120·0	322·0	989·0	
Titre (ml.)	11·60	15·20	16·30	16·79	16·97	16·99	17·02	17·26	

By a method analogous to that used for the calculation of the composition of the product of chlorination, it was found that the product of bromination contained 82% of secondary bromide. First-order rate coefficients were calculated as before.

Hydrolysis of the Monobrominated Material, at Room Temperature, in the Presence of Silver Nitrate.—The product (0·1161 g.) was dissolved in 80% aqueous ethyl alcohol (50 ml.), and standard silver nitrate solution (10 ml. of 0·0963N) added. After the mixture had been shaken for 30 min. at room temperature (21°), the solid silver bromide was filtered off and washed with dilute nitric acid. The filtrate and washings were titrated with standard ammonium thiocyanate solution (31·11 ml. of 0·0212N were required), by Volhard's method.

It was calculated that 54% of the bromide had reacted, whereas in the absence of silver nitrate no reaction had taken place.

I thank Professors Sir Christopher Ingold, F.R.S., and E. D. Hughes, F.R.S., for their interest and encouragement.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER STREET, LONDON, W.C.1. [*Received, April 29th*, 1959.]

[9] Guggenheim, *Phil. Mag.*, 1926, **7**, 538.

704. *Infrared Absorption of Heteroaromatic, Five-membered, Monocyclic Nuclei. Part II.*[1] *2-Monosubstituted Thiophens.*

By A. R. Katritzky and A. J. Boulton.

The positions and intensities of nine characteristic bands are recorded and discussed for thirteen 2-monosubstituted thiophens.

2-Monosubstituted furans show characteristic absorption bands which could be assigned to specific normal vibrations of the furan nucleus.[1] We have now extended this work to the corresponding thiophens. In the region of the spectrum investigated, 2000—800 cm.$^{-1}$, absorption corresponding to the modes (I—XI) might be found. As before,[1] the positions of the ring stretching modes (I—IV) and the ring breathing mode (VIII) should be similar to those in thiophen itself, and the positions of the CH-in-plane (IV—VII) and the CH-out-of-plane deformation modes (IX—XI) to those of vicinal trisubstituted benzenes.

Ring Stretching Frequencies at 1600—1300 *cm.*$^{-1}$.—Thiophen shows bands at 1591 cm.$^{-1}$ (8), 1409 cm.$^{-1}$ (32), and 1255 cm.$^{-1}$ (43) * in the infrared and an additional band at 1358 cm.$^{-1}$ in the Raman spectrum,[2] which were assigned to vibrations (I)—(IV) respectively. The bands shown by the substituted thiophens at 1537—1509 [1523 ± 9],† 1444—1402 [1422 ± 12], 1365—1339 [1354 ± 7], and 1258—1220 cm.$^{-1}$ (30—155) [1231 ± 10 cm.$^{-1}$ (80 ± 30)] (Table, cols. 1—4) are therefore assigned to modes (I)—(IV), respectively. The intensities of the first three bands are less when the ring is attached to weakly electron-accepting substituents {for Nos. 1—8 the intensities are respectively (3—30) [(15 ± 5)], (20—115) [(75 ± 35)], and (15—60) [(25 ± 20)]} than when the ring is attached to strong electron acceptors {for Nos. 9—13, intensities are (50—110) [(85 ± 30)], (120—280) [(190 ± 60)], and (45—150) [(95 ± 35)]}. This pattern of intensity variation is expected, for the thiophen ring is a strong electron donor and large interactions between ring and substituent are known to intensify ring stretching bands.[1,3]

Hydrogen In-plane Deformations at 1250—1000 *cm.*$^{-1}$.—The bands at 1086—1077 cm.$^{-1}$ (5—20) [1081 ± 3 cm.$^{-1}$ (10 ± 5)], and 1053—1031 cm.$^{-1}$ (5—110) [1043 ± 7 cm.$^{-1}$ (55 ± 40)] (Table, cols. 5—6) probably correspond to the modes (VI) and (VII). In vicinal trisubstituted benzenes [4] the corresponding modes absorb near 1160 and 1073 cm.$^{-1}$, and in 2-substituted furans [1] near 1158 and 1076 cm.$^{-1}$. The mode (V) probably occurs near 1200 cm.$^{-1}$ (cf. vicinal benzenes) and is possibly obscured by mode (IV).

Hydrogen Out-of-plane Deformations below 1000 *cm.*$^{-1}$.—The bands at 938—905 cm.$^{-1}$ (5—20) [925 ± 8 cm.$^{-1}$ (10 ± 5)] and 863—841 cm.$^{-1}$ (45—110) [853 ± 7 cm.$^{-1}$ (75 ± 25)] probably correspond to modes (IX) and (X); mode (XI) is probably obscured by solvent absorption below 800 cm.$^{-1}$. The corresponding bands for vicinal trisubstituted benzenes [4] absorb near 958, 893, and 770 cm.$^{-1}$ and for 2-substituted furans [1] near 925, 884, and below 800 cm.$^{-1}$.

Ring Breathing Frequency.—The band at 831 cm.$^{-1}$ (95) for thiophen has been assigned to mode (VIII).[2] The 2-substituted derivatives all show a band at 839—790 cm.$^{-1}$ (25—85) [823 ± 20 cm.$^{-1}$ (50 ± 20)] (Table, col. 9) which is accordingly assigned to this mode.

* Measured in $CHCl_3$ solution at 0·700M.

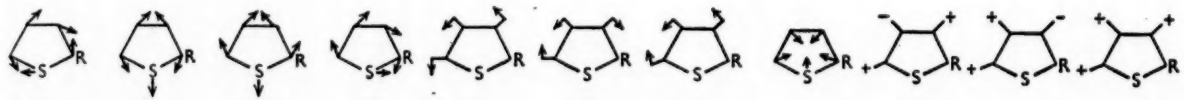
† Apparent extinction coefficients are in parentheses and arithmetic means and standard deviations in brackets. The intensities of shoulders and superimposed bands and the positions of shoulders are not treated statistically.

[1] Part I, Katritzky and Lagowski, *J.*, 1959, 657.

[2] (*a*) Thompson and Temple, *Trans. Faraday Soc.*, 1945, **41**, 27; (*b*) Waddington *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 797; (*c*) Lecomte, *Bull. Soc. Chim. France*, 1946, 415; (*d*) Hidalgo, *J. Phys. Radium*, 1955, **16**, 366.

[3] Katritzky, *J.*, 1958, 4162.

[4] Randle and Whiffen, Paper No. 12, Report of the Conference of Molecular Spectroscopy, 1954. Institute of Petroleum.



(I) (II) (III) (IV) (V) (VI) (VII) (VIII) (IX) (X) (XI)

		1		2		3		4		5		6		7		8		9		10	11	12
		B_1		A_1		A_1		B_1		B_1		A_1		B_2		A_2		A_1				
		νC–C		νC–C		νC–C		νC–C		βCH		βCH		γCH		γCH		ring				
		νC–S		νC–S		νC–S		νC–S										breath				
No.	Subst.	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	B. p.	mm.	Ref.
1	Me*	1537	3	1444	45	—		1239	40	1078	15	1043	12	938	5	846	50	817	45	112—113°	760	*a*
2	Ph*	1533	15	1433	20	1353	5	1258	30	1081	15	1047	5	905	10	849	75	826	30	37—39°	*b*	*a*
3	Cl	1518	30	1415	115	1347	10	1220	95	1085	10	1052	80	923	5	842	85	819	60			*c*
4	Br	1509	20	1405	95	1339	10	1220	80	1080	5	1044	25	926	5	841	85	819	55	56°	26	*d*
5	CH:CH·CO_2Me	1518	15	1428	110	1365	60	1230	100	1078	5	1043	90	923	20	855	110	827	85	47—48°	*b*	*e*
6	CH:CH·CO_2Et	1517	15	1428	60	(—)		1230	115	(—)		1042‡	160	926	5	855	110	828	90	109—111°	1·3	*f*
7	CMe:NOH	1532	15	1433	55	1352	25	($CHCl_3$)		1086	20	1036†	20	(—)		850	65	828	50	117·5—118°	*b*	*g*
8	CH:NOH	1514	15	1424	90	1352	30	1230	55	1077	5	1053	55	(—)		856	45	825	30	132·5—134°	*b*	*h*, *i*
9	CO_2Me	1527	110	1418	120	1362	150	1225	60	(—)		1040	20	929	20	857	90	786	50	89—90°	17	*j*
10	CO_2Et	1528	110	1422	220	1357	75	1225	75	(—)		1042	40	923	5	859	55	810	25	101—102°	17	*j*
11	CHO	1517	50	1422	190	1358	45	1230	155	1082	10	1047	110	925	10	863	45	839	40	84°	17	*k*
12	COMe	1514	70	1415	280	1356	110	1230	80	1082	20	1032	35	932¶	50	858	95	839	35	57—58°	0·7	*l*
13	NO_2	1532	220‡	1402	130	1365‡	200	($CHCl_3$)		1083	5	1031	110	924	10	857	75	834	35	43°	*b*	*m*

* Measured in 0·700M solution. † Shoulder. ‡ Intensity of peak materially raised by overlap with another band. — Absence of absorption. (—) Band masked by stronger absorption. ¶ Peak considered to be the result of the superimposition of two bands.

The approximate symmetry type is given beneath the column number, those in cols. 1—3 and 9 by analogy with unsubstituted thiophen, and those in cols 5—8 by analogy with vicinal trisubstituted benzenes; see text.

Compounds were prepared by the methods indicated in the references (except for Nos. 3, 4, 11, 12, and 13 which were commercial products and Nos. 5 and 6 which were prepared as indicated in footnote *e*). The physical constants quoted (cols. 10—11) were in agreement with literature values as also were refractive indices of the liquid compounds.

a Kues and Paal, *Ber.*, 1886, **19**, 556, 3142. *b* M. p. *c* Weitz, *Ber.*, 1884, **17**, 794. *d* Krause and Renwanz, *Ber.*, 1929, **62**, 1710. *e* 3-(2-Thienyl-)acrylic acid (1·0 g.) was refluxed for 6 hr. with methanol (25 c.c.) and sulphuric acid (2·5 c.c.). The cooled mixture was poured into water (150 c.c.) and extracted with ether. Drying ($MgSO_4$), evaporation of solvents, and distillation gave the *methyl ester* (b. p. *ca.* 100°/0·1 mm.; 0·7 g., 65%) which solidified on cooling, and after four crystallisations from light petroleum (b. p. 60—80 °), had m. p. 47—48° (Found: C, 57·3; H, 5·2. $C_8H_8O_2S$ requires C, 57·1; H, 4·8%). *f* King and Nord, *J. Org. Chem.*, 1949, **14**, 405. *g* Peter, *Ber.*, 1884, **17**, 2644. *h* Biedermann, *Ber.*, 1886, **19**, 1854. *i* Goldschmidt and Zanoli, *Ber.*, 1892, **25**, 2588. *j* Weinstein, *J. Amer. Chem. Soc.*, 1955, **77**, 6709. *k* Biedermann, *Ber.*, 1886, **19**, 638. *l* Johnson and May, *Org. Synth.*, 1938, **18**, 1. *m* Meyer and Stadler, *Ber.*, 1884, **17**, 2648.

Substituent Bands.—Most of the remaining bands with $\varepsilon_A > 10$ could be assigned to substituent absorption, but the bands shown by No. 1 at 1163 cm.$^{-1}$ (30), by No. 2 at 955 cm.$^{-1}$ (15), by No. 12 at 1016 cm.$^{-1}$ (20), and by No. 13 at 1433 cm.$^{-1}$ (25) were anomalous.

Previous Work.—Hidalgo [2d] measured six 2-substituted thiophens (as liquid films) (substituents; Me, Et, Br, Cl, Ac, CH:CH_2) and recorded twelve bands as characteristic of the nucleus. Three of these occur below 800 cm.$^{-1}$; eight of the remaining nine correspond to those given in the Table, cols. 1—6, 8—9. There is good overall agreement between results, but the frequency ranges quoted by Hidalgo are mostly considerably greater than ours. We have not found the band quoted [2d] at 1355—1236 cm.$^{-1}$; Hidalgo does not report the band that we find at 938—923 cm.$^{-1}$.

Hochgesang,[5] who summarises early work, recorded the spectra of ten 2-substituted thiophens (Me, Et, CH:CH_2, Pr^n, Bu^n, Bu^t, Cl, Br, Ac, and SH), mainly as liquid films. The positions agree well with those in this paper; no precise intensities were quoted. The generalisations made are, as far as they go, in accord with the present results.

Experimental.—See Ref. 1 for conditions of measurement.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, May 15th,* 1959.]

[5] Hochgesang, in Hartough, " Thiophene and its Derivatives," Interscience Inc., 1952.

---

705. *Phenacyl Sulphides and Related Compounds. Part I. The Action of Alkali on o-Nitrophenyl Phenacyl Sulphide.*

By K. J. MORGAN.

A large number of compounds is formed by the action of alkali on *o*-nitrophenyl phenacyl sulphide. The most abundant products correspond to the displacement of the *o*-nitrothiophenoxy-group and to reductive cyclisation to benzothiazole derivatives. Smaller amounts of material obtained by fission on either side of the carbonyl group are detected.

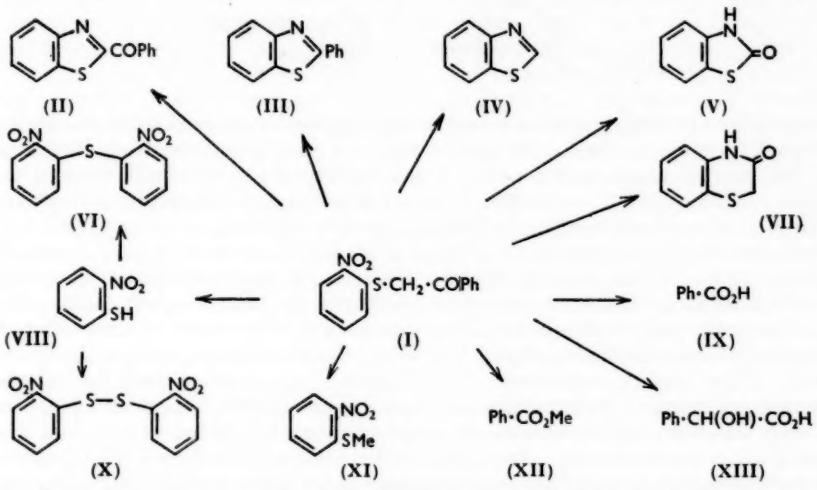
ALTHOUGH simple sulphides are stable to alkali [1] the presence of a carbonyl group adjacent to the sulphide bond renders it labile. Nucleophilic attack then displaces the sulphur grouping from the carbonyl moiety in such molecules to give thiols, sulphides, or elemental sulphur.[2] Also susceptible to nucleophilic attack are nitro-substituted aryl sulphides which decompose in alkaline methanol with the formation of nitroanisoles.[3] It seemed of interest to examine the behaviour under alkaline conditions of *o*-nitrophenyl phenacyl sulphide (I) since it appeared possible that fission of the two sulphur–carbon bonds would proceed competitively.

o-Nitrophenyl phenacyl sulphide was prepared from the corresponding sulphenyl chloride and acetophenone.[4] Preliminary experiments indicated that the action of alkali on this gave products more complex than the simple displacement reactions had suggested. Eventually some dozen products (II—XIII) were isolated and identified; the variation in yield of the more abundant of these with the reaction conditions is shown in the Table. A careful examination of the products failed to detect any *o*-nitroanisole or ω-mercaptoacetophenone and from the structure of those compounds that were found it is apparent that there was no displacement of sulphur from the aromatic ring. The two main reactions involve fission of the sulphur–methylene bond and reductive cyclisation of the whole molecule severally. In addition, smaller amounts of products derived from fission on

[1] See, *e.g.*, Bilheimer and Reid, *J. Amer. Chem. Soc.*, 1930, **52**, 4338.
[2] See, *e.g.*, Schönberg and Iskander, *J.*, 1942, 90; Vinkler and Autheried, *Acta Univ. Szeged Chem. et Phys.*, 1948, **2**, 105; Banfield, Davies, Gamble, and Middleton, *J.*, 1956, 4791.
[3] Kharasch and Swidler, *J. Org. Chem.*, 1954, **19**, 1704.
[4] Kharasch, Wehrmeister, and Tigerman, *J. Amer. Chem. Soc.*, 1947, **69**, 1612; Barltrop and Morgan, unpublished work.

either side of the carbonyl group are found. The facility with which these reactions occur—the molecule is sensitive even to cold sodium carbonate solution—is particularly striking.

The main cleavage reaction is that expected for nucleophilic displacement of the *o*-nitrothiophenoxyl ion, which is assisted by the mesomeric influence of the nitro-group.



The results indicate that the order of reactivity of the basic ions is $HO^- > MeO^- > Bu^tO^-$, and this may be ascribed partly to a steric factor and partly to the possibility of a hydrogen-bonded transition state [5] (XIV; R = S·C$_6$H$_4$·NO$_2$) in which case hydroxyl ion is the

Effect of reaction conditions on the products formed in the alkaline decomposition of o-nitrophenyl phenacyl sulphide.

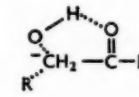
Reagent	KOH 3 equiv.	KOH 1 equiv.	KOH 1 equiv.	Na_2CO_3 [a] 1 mol.	KOMe 1 equiv.	KOBu^t 1 equiv.
Solvent	MeOH	MeOH	MeOH	MeOH	MeOH	Bu^{t}OH
Temp.	65°	65°	20°	20°	65°	82°
Time (hr.)	2	0·5	24	24	0·5	0·5
Product	Yield (%)					
o-Nitrothiophenol [b]	34·5	49·7	45·1	36·5	35·0	25·3
o-Nitrophenyl sulphide	1·3	2·2	2·7	3·0	2·2	2·5
Benzoic acid	58·9	26·0	30·1	24·9	3·4	51·1
2-Benzoylbenzothiazole	19·2	30·6	23·3	12·3	27·0	6·5
2-Phenylbenzothiazole	8·6	3·0	2·0	0·4	0·7	1·8
Benzothiazole	6·2	4·7	2·7	2·6	6·7	18·9
Me benzoate	0	4·9	3·6	6·7	9·0	0
o-Nitrothioanisole	2·6	2·8	2·1	3·3	2·6	2·5

[a] 24·3% of starting material was recovered; yields are calculated on the basis of material consumed. [b] Total amounts of thiol (VIII) and disulphide (X) are listed together.

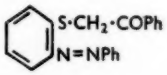
effective agent. (The low yield of disulphide when three mols. of potassium hydroxide are used is due to its decomposition; it is largely stable under the conditions used in the other experiments.) Oxidation during the analysis of the products prevented accurate estimation of the relative amounts of *o*-nitrothiophenol (VIII) and of the corresponding disulphide (X) which were formed directly in the reaction; it was noticeable that as the conditions became less vigorous the combined amount of thiophenol and disulphide isolated

[5] Cf. Baddeley, *Ann. Reports*, 1955, **52**, 150.

from the crude acidic fraction fell. Also derived from *o*-nitrothiophenol is di-*o*-nitrophenyl sulphide (VI), formed by anionic attack of the thiophenoxy-ion, a powerfully nucleophilic reagent, on the free thiophenol; [6] its uniformly low yield may be due in part to its partial decomposition under the reaction conditions.



(XIV)



(XV)

Formation of *o*-nitrothiophenol should be accompanied by the production of ω-hydroxy- and ω-alkoxy-acetophenones. No such compounds were found; instead, benzoic acid (IX) was isolated in comparable yield. The instability of ω-hydroxyacetophenone under alkaline conditions is well established: [7] by a reverse benzoin reaction benzaldehyde and thence benzoic acid are formed. ω-Methoxyacetophenone with potassium hydroxide in methanol similarly gives benzoic acid, the yield of which is increased in the presence of an oxidising agent. In the absence of water ω-methoxyacetophenone is largely stable to anhydrous alcoholic alkali; ω-phenoxyacetophenone behaves similarly. The efficacy of the less nucleophilic hydroxyl ion in this reaction is best described by a transition state stabilised by hydrogen-bonding (XIV; R = OMe) which leads irreversibly to the hydroxy-ketone. When the decomposition of *o*-nitrophenyl phenacyl sulphide in anhydrous methanol was examined the usual large amounts of benzoic acid or ω-methoxyacetophenone were not isolated; and when ω-methoxyacetophenone was added at the start of the reaction it too was consumed. The ready condensation of ω-methoxyacetophenone with carbonyl compounds has been used synthetically [8] and it seems probable that an analogous reaction occurs here. Examination of the unresolved tarry residues revealed the presence of ketonic materials, but these could not be purified. Conversely, when dry t-butyl alcohol was used as solvent a considerable quantity of benzoic acid was formed, part of which must be derived from fission of the sulphur–methylene bond. The ability of t-butyl compounds to decompose with *O*-alkyl fission suggests that here *O*-alkyl rather than *O*-phenacyl fission of the initially formed t-butoxyacetophenone leads directly to the anion of ω-hydroxyacetophenone which can then decompose in the usual way. Accompanying the benzoic acid from the reaction in t-butyl alcohol is a smaller amount of mandelic acid (XIII). It seems probable that the lack of reducing properties of t-butyl alcohol permits the oxidation of part of the phenacyloxy-ion to phenylglyoxal which in alkaline solution tautomerises to mandelic acid.[9]

The formation of small amounts of *o*-nitrothioanisole (XI) and methyl benzoate (XII) indicates that some attack must occur directly at the carbonyl group. In moist methanol, methyl benzoate is partially hydrolysed under the reaction conditions but the possibility that such an attack could produce the majority of the benzoic acid may be discounted: the small amount of *o*-nitrothioanisole cannot be reconciled with such a decomposition; neither can the comparatively small increase in yield of methyl benzoate found under anhydrous conditions. It is noteworthy that in t-butyl alcohol no t-butyl benzoate is detected although the usual small quantity of *o*-nitrothioanisole is formed. Unimolecular *O*-alkyl fission of t-butyl benzoate has been reported,[10] and it seems probable that such a decomposition occurs here. A similar bimolecular *O*–alkyl fission [11] may account for part of the small quantity of benzoic acid formed in anhydrous methanol.

[6] Cf. Cole, *Chem. and Ind.*, 1957, 1511.
[7] Zincke and Hunaeus, *Ber.*, 1877, **10**, 1486; Zincke, *Annalen*, 1883, **216**, 308; King, *J. Amer. Chem. Soc.*, 1944, **66**, 894.
[8] See, *e.g.*, Pratt and Robinson, *J.*, 1923, **123**, 748; Malkin and Robinson, *J.*, 1925, **127**, 372.
[9] Müller and von Pechmann, *Ber.*, 1889, **22**, 2556; Nef, *Annalen*, 1904, **335**, 247.
[10] Cohen and Schneider, *J. Amer. Chem. Soc.*, 1941, **63**, 3387.
[11] Bunnett, Robinson, and Pennington, *ibid.*, 1950, **72**, 2378.

A small amount of dihydro-oxobenzothiazine (VII) corresponding to fission between the phenyl and the carbonyl group was isolated, but only from the reaction in dry methanol. Reduction with zinc and acetic acid of *o*-nitrophenylthioacetic acid (which was not found among the products) leads directly to this lactam,[12] but under the conditions used here the nitro-acid is stable. Consequently, reduction of the nitro-group must precede the fission. Anionic cleavage of the carbon–carbon bond can then give the amino-ester, which through the lactam gives the water-soluble salt of the free amino-acid; the lactam is regenerated on acidification.[13] This route is preferred to cyclisation of the amino-ketone and subsequent fission of the carbon–carbon bond since no 3-phenylbenzothiazine is detected and acidic reduction of *o*-nitrophenyl phenacyl sulphide [14] gives no dihydro-oxobenzothiazine. The formation of this benzothiazine derivative must proceed competitively with the formation of the benzothiazole compounds discussed below; its occurrence only in dry methanol can be ascribed, first, to the decreased amount of carbon–sulphur fission and, secondly, to the relatively strongly reducing properties of this medium.

The second group of products is formed in reductive cyclisations and all contain a benzothiazole ring. The most abundant of these is 2-benzoylbenzothiazole (II) formed in good yield by reductive condensation of the nitro-group and the α-methylene group. The ready reduction of nitro-compounds under alkaline conditions [15] and the ease with which nitroso-compounds condense with active methylene groups [16] indicate the mechanism of this reaction; the considerable amounts of benzothiazole derivatives found when t-butyl alcohol is used as solvent are of additional interest in showing that much of the necessary reduction is effected by the sulphide group rather than the alcoholic substrate. A close analogy is provided by the cyclisation under alkaline conditions of *o*-nitrophenylacetaldehyde to give indole.[17] 2-Benzoylbenzothiazole is also formed by cyclisation under acidic conditions of phenacyl 2-phenylazophenyl sulphide (XV).[18] The two reactions are closely related: in each case an electron-deficient nitrogen group condenses with the reactive methylene group.

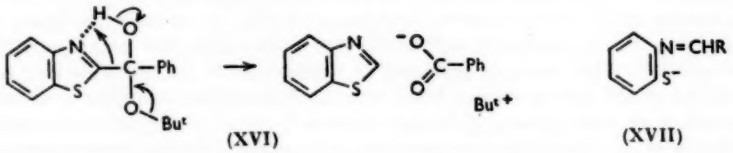
2-Benzoylbenzothiazole is largely stable in alkaline methanol but a small amount of decomposition to benzothiazole (IV) and benzoic acid does occur. The results suggest that this carbonyl fission is of similar importance to that producing *o*-nitrothioanisole. In t-butyl alcohol this reaction occurs more readily and consumes practically all the ketone. A similar fission of benzophenone with potassium t-butoxide has been reported [19] although benzophenone is completely resistant to attack by alkaline methanol. The efficacy of t-butoxide ions in promoting this reaction is best accommodated in a cyclic mechanism (XVI): separation of the t-butyl ion is supposed to occur simultaneously with fission of the carbon–carbon bond and so initiates the complete reaction sequence. Hydrogen-bonding of the hydroxyl group to the heterocyclic nitrogen atom must help by localising the hydrogen ion and also accounts for the conversion into benzoic acid rather than into a mixture with benzothiazole-2-carboxylic acid.

The isolation of small amounts of 2-phenylbenzothiazole (III) implies a rather different cyclisation. The product contains one less carbon atom than the starting material, and this suggests that fission precedes cyclisation. The formation of benzothiazoles by the condensation of *o*-aminothiophenol and carbonyl compounds represents a conventional synthetic route.[20] Treatment of *o*-nitrothiophenol with benzaldehyde in alkaline methanol gives small amounts of 2-phenylbenzothiazole and so indicates that this can provide the

[12] Friedländer and Chwala, *Monatsh.*, 1907, **28**, 247.
[13] Culvenor, Davies, and Heath, *J.*, 1949, 278.
[14] Zincke and Baeumer, *Annalen*, 1918, **416**, 86.
[15] See, *e.g.*, Simons and Ratner, *J.*, 1944, 421.
[16] See, *e.g.*, Ehrlich and Sachs, *Ber.*, 1899, **32**, 2341; Walker, *J.*, 1924, **125**, 1622.
[17] Weerman, *Annalen*, 1913, **401**, 10.
[18] Burawoy and Chaudhuri, *J.*, 1956, 648.
[19] Swan, *J.*, 1948, 1408.
[20] Hofmann, *Ber.*, 1880, **13**, 1236; Lankelma and Sharnoff, *J. Amer. Chem. Soc.*, 1931, **53**, 2654; 1932, **54**, 379.

XUM

effective route. Further support for this mechanism is given by the occurrence of 2-phenylbenzothiazole only in the alkali-soluble fraction. Bogert and Naiman [21] have shown that the anil (XVII) is formed in alkaline solution and rearranges to the thiazolidine only when the free thiol is liberated; aromatisation to the thiazole is completed by autoxidation.



(XVI) (XVII)

Benzothiazolin-2-one (V), found in small yield in the reaction in sodium carbonate solution, may well be formed in a similar reaction with carbonate ion or carbon dioxide.

Apart from the compounds isolated and identified, two orange solids, m. p. 151° and 243° respectively, were isolated; these have not been identified. There remained unresolved a considerable quantity of tar which is receiving further investigation.

Experimental

Methanol and ethanol were dried with magnesium; t-butyl alcohol was dried with lithium aluminium hydride.

Action of Alkali on o-*Nitrophenyl Phenacyl Sulphide.*—A solution of sulphide [4] (9·1 g.), m. p. 145° (from acetonitrile), in dry methanol (250 c.c.) containing potassium methoxide (from potassium, 1·3 g., 1 equiv.) was boiled under reflux for 30 min. The solution was chilled and the solvent removed *in vacuo*. The residue was partitioned between water (100 c.c.) and ether (3 × 100 c.c.); the aqueous phase was washed with ether (4 × 50 c.c.) and the ethereal extracts were combined.

(a) *Aqueous extract.* Acidification and extraction with chloroform gave a black tar (3·5 g.) from which hot water extracted *o*-nitrothiophenol (20 mg.), m. p. 54° [from carbon tetrachloride–light petroleum (b. p. 40—60°)], benzoic acid (90 mg.), m. p. 121° (from water), and 3,4-dihydro-3-oxo-2*H*-benzothiazine (160 mg.), m. p. 177—178° (after sublimation). The water-insoluble residue (3·2 g.) was extracted into ether; *o*-nitrophenyl disulphide (350 mg.), m. p. 199° (from benzene), remained as an insoluble residue. Washing the ethereal extract with alkali gave further quantities of *o*-nitrothiophenol (900 mg.), benzoic acid (50 mg.), and dihydro-oxobenzothiazine (150 mg.). Chromatography of the residual ethereal extract on alumina gave the following fractions: (i) 2-phenylbenzothiazole (50 mg.), m. p. 114° (from methanol), eluted with light petroleum; (ii) 2-benzoylbenzothiazole (120 mg.), m. p. 105° (from methanol), eluted with light petroleum–benzene; (iii) *o*-nitrophenyl disulphide (200 mg.), eluted with light petroleum–benzene; and an unidentified tarry residue.

(b) *Ethereal extract.* Evaporation of the ether left an oil (5·4 g.) whcih was steam-distilled. The distillate (1·2 g.) gave methyl benzoate (400 mg.), b. p. 79°/10 mm., and benzothiazole (230 mg.), b. p. 110°/10 mm., as readily distillable fractions which left a mixture of 2-benzoylbenzothiazole (80 mg.), and *o*-nitrothioanisole (150 mg.), m. p. 63° (from methanol), separated by chromatography on alumina. The steam non-volatile residue (4·2 g.) was chromatographed on alumina to give the following fractions: (i) benzoylbenzothiazole (1·95 g.); (ii) *o*-nitrophenyl disulphide (125 mg.); (iii) *o*-nitrophenyl sulphide (100 mg.), m. p. 123° (from ethanol); (iv) an orange solid (50 mg.), m. p. 151° (from methanol), $\lambda_{max.}$ 253 (log ε 4·40), 330 mμ (log ε 3·85) in methanol (Found: C, 74·1; H, 4·2; S, 10·4. Calc. for $C_{18}H_{13}ONS$: C, 74·2; H, 4·5; S, 11·0%); this was not identical with azo-*o*-anisole or azo-*o*-thioanisole; (v) an orange solid (60 mg.), m. p. 243° (from methanol), $\lambda_{max.}$ 266 (log ε 4·33), 310 mμ (log ε 3·68) in methanol (Found: C, 71·0; H, 4·7; S, 12·6. Calc. for $C_{15}H_{13}ONS$: C, 70·6; H, 5·1; S, 12·6%); (vi) tarry fractions showing carbonyl bands in their infrared spectra.

In each case the identity of the product was confirmed by comparison of infrared spectra.

[21] Bogert and Naiman, *J. Amer. Chem. Soc.*, 1935, **57**, 1529.

With appropriate modifications this analysis was applied to each set of reaction conditions. Dihydro-oxobenzothiazine was found in no other experiment; mandelic acid (400 mg., 7·4%), m. p. 120° (from benzene), was obtained from the reaction in t-butyl alcohol; benzothiazolin-2-one (150 mg., 5%), m. p. 136° (from aqueous ethanol), was found only in the reaction with sodium carbonate. No reaction occurred with sodium acetate or with sodium formate in methanol at 20° for 24 hr.

Action of Alkali on 2-Benzoylbenzothiazole.—The ketone, colourless needles, m. p. 107° (from methanol) (lit.,[22] m. p. 102·5°) (Found: C, 69·9; H, 3·7; N, 6·0; S, 13·5. Calc. for $C_{14}H_9ONS$: C, 70·3; H, 3·8; N, 5·9; S, 13·4%), gave an *oxime*, m. p. 168° (from methanol) (Found: C, 66·1; H, 3·9. $C_{14}H_{10}ON_2S$ requires C, 66·1; H, 4·0%), and a *2,4-dinitrophenylhydrazone*, m. p. 248° (from benzene) (Found: C, 57·5; H, 3·2. $C_{20}H_{13}O_4N_5S$ requires C, 57·3; H, 3·1%).

(i) *Action of alkaline methanol.* 2-Benzoylbenzothiazole (190 mg., 90%) was recovered after being boiled with methanol (25 c.c.) and potassium hydroxide (1·0 g.) for 2 hr. Benzoic acid (5 mg.) was obtained.

(ii) *Action of alkaline t-butyl alcohol.* 2-Benzoylbenzothiazole (750 mg.) was boiled under reflux with potassium t-butoxide (from potassium, 650 mg.) in t-butyl alcohol (150 c.c.) for 30 min., giving benzoic acid (350 mg., 81%) and benzothiazole.

2-Phenylbenzothiazole.—A solution of *o*-nitrothiophenol (2 g.), benzaldehyde (4 g.), and potassium hydroxide (5 g.) in methanol (250 c.c.) was boiled for 2 hr., to give 2-phenylbenzothiazole (100 mg.), m. p. 114° (from methanol) (Found: C, 73·9, 73·8; H, 4·2, 4·3. Calc. for $C_{13}H_9NS$: C, 73·9; H, 4·3%); benzoic acid is formed in large amounts. A higher yield (230 mg.) was obtained by adding zinc (1·0 g.) to the reaction mixture.

Action of Alkali on ω-Methoxyacetophenone.—The ketone,[8] b. p. 115°/12 mm., gave a 2,4-dinitrophenylhydrazone, m. p. 198° (from methanol–methyl acetate) (lit.,[23] m. p. 192—194°). (i) A solution of ketone (1·35 g.) in methanol (125 c.c.) containing potassium hydroxide (2·8 g.) was boiled under reflux for 30 min., giving benzoic acid (300 mg.). (ii) A similar mixture containing additionally *o*-nitroanisole (1·2 g.) gave benzoic acid (800 mg.). (iii) Ketone (1·2 g., 96%) was recovered after being boiled in dry methanol (120 c.c.) containing potassium methoxide (from potassium, 0·5 g.) for 30 min. (iv) Ketone (0·9 g. 65%) was recovered after being boiled under reflux in dry ethanol (120 c.c.) containing potassium ethoxide (from potassium, 0·5 g.) for 44 hr. (v) A mixture of ketone (2 g.) and *o*-nitrophenyl phenacyl sulphide (7·0 g.) in dry methanol containing potassium methoxide (from potassium, 1·0 g.) was boiled for 30 min. Examination of the products in the usual way (omitting the steam-distillation) failed to detect any ω-methoxyacetophenone.

Action of Alkali on ω-Phenoxyacetophenone.—Ketone [24] (2·25 g., 98%), m. p. 72° (2,4-dinitrophenylhydrazone, m. p. 188—190°), was recovered after being boiled for 45 hr. with 0·1N-potassium methoxide in methanol (120 c.c., 1·25 equiv.). The ketone (2·25 g.), boiled under reflux for 2 hr. with 0·16N-potassium hydroxide in methanol (120 c.c., 2 equiv.), gave benzoic acid (25 mg.); after 40 hr., benzoic acid (0·3 g.) and phenol, characterised as tribromophenol (0·8 g.), m. p. 91—93°, were formed.

Stability of Nitro-compounds under Reaction Conditions.—*o*-Nitrothioanisole and *o*-nitrophenylthioacetic acid were stable under all reaction conditions; *o*-nitrophenyl disulphide was stable to all but 3 equiv. of potassium hydroxide, *o*-nitrophenyl sulphide was partially decomposed by boiling 0·2N-methanolic potassium hydroxide in 30 min.

Infrared spectra were measured on a Perkin–Elmer Model 21 spectrophotomer; the spectra will be deposited in the D.M.S. collection.

Part of this work was performed during the tenure of an I.C.I. Fellowship. The author thanks Dr. J. A. Barltrop and Dr. E. J. Forbes for helpful discussions.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, May 19th,* 1959.]

[22] Gilman and Beel, *ibid.*, 1949, **71**, 2328.
[23] Yates, *J. Amer. Chem. Soc.*, 1952, **74**, 5376.
[24] Davies and Middleton, *J.*, 1958, 822.

XUM

706. *The Reaction of* 1,3,5-*Trinitrobenzene with Aliphatic Amines.*

By R. Foster.

Spectrophotometric study of the interaction of 1,3,5-trinitrobenzene with a series of aliphatic amines in chloroform and dioxan discloses, in most cases, a fast reaction (which may be a charge-transfer complex interaction) and a slow reaction. Job continuous-variation plots indicate that for methyl-, ethyl-, dimethyl-, and diethyl-amine the molar ratio amine : trinitrobenzene is 3 : 1, for both reactions, whereas for more bulky amines the stoicheiometry is 1 : 1.

1,3,5-Trinitrobenzene behaves as a Lewis acid in interactions with aromatic hydrocarbons and aromatic amines. Mulliken [1] has described the results of these reactions, both in solution and in the solid state, as charge-transfer complexes. The forces involved include local dipole and dispersion forces together with a contribution from a covalent structure in which an electron has been donated from the π-molecular orbital of the hydrocarbon or amine molecule to an anti-bonding π-orbital of the trinitrobenzene molecule. These complexes have characteristic absorption bands. Most observations of these complexes in solution are in accordance with the assumption that only 1 : 1 complexes are formed, although in at least one case it has been suggested [2] that there are contributions from complexes with aromatic amine : trinitrobenzene ratios also of 2 : 1 and 1 : 2. Orgel and Mulliken [3] recently suggested that there may be absorption from donor–acceptor pairs in ephemeral contact as well as from those which are held together for a finite time as discrete complexes.

The absorption bands characteristic of the complex do not alter with time, and complex formation of the above type must therefore be very fast.

By contrast, colour develops slowly when trinitrobenzene is mixed with aliphatic amines. Such solutions in chloroform or dioxan develop absorption bands in the region 420—600 mμ. The actual maxima are difficult to determine owing to the broadness of the bands and their dependence on time. There is often more than one maximum. There is no simple relation between the frequency of the absorption maxima of these complexes and the ionisation potentials of the component aliphatic amines (Table 1), whereas a linear relation normally exists between the frequency of the charge-transfer bands of complexes of a given acceptor and the ionisation potentials of the component aromatic amine or aromatic hydrocarbon molecules.[4]

Table 1. *Frequencies* (ν) *of the absorption band of the adduct of various amines with trinitrobenzene in chloroform measured several hours after mixing, and the ionisation potentials* (*Ip*).

Base	ν (cm.$^{-1}$)	*Ip* (ev) [a]	Base	ν (cm.$^{-1}$)	*Ip* (ev) [a]
NH_3	21,000	10·15	NMe_3	24,000	7·82
NH_2Me	23,000, 20,000	8·97	$CH_2Ph{\cdot}NH_2$	21,000	7·56
$NHMe_2$	21,000	8·24			

[a] Watanabe and Mottl, *J. Chem. Phys.*, 1957, **26**, 1773.

The rate of development depends on the amines, the order being ammonia $\ll$ methylamine $>$ dimethylamine $\gg$ trimethylamine. Ultimately, a relatively stable colour is obtained. After several hours trinitrobenzene can be recovered quantitatively by acidification or precipitation, although after several days an irreversible reaction occurs. In most cases plots of optical absorption with time against the time of mixing indicate that a substantial colour often develops immediately and is followed by further slow development (see Figures 1 and 2).

[1] Mulliken, *J. Amer. Chem. Soc.*, 1950, **72**, 605; 1952, **74**, 811; *J. Phys. Chem.*, 1952, **56**, 801.
[2] Ross and Labes, *J. Amer. Chem. Soc.*, 1957, **79**, 76.
[3] Orgel and Mulliken, *ibid.*, p. 4839.
[4] McConnell, Ham, and Platt, *J. Chem. Phys.*, 1953, **21**, 66; Briegleb and Czekalla, *Z. Electrochem.*, 1955, **59**, 184; Bier, *Rec. Trav. chim.*, 1956, **75**, 866.

Previous work [5] on the intensity of the band at 475 mμ of mixtures of varying composition appeared to show that the interaction of dimethylamine with trinitrobenzene involves a 4 : 1 ratio of the two components, but this has been re-interpreted by Ross and Labes [6] as a 3 : 1 association. We have confirmed the 3 : 1 ratio for this system and have determined the ratio for other aliphatic amine–trinitrobenzene systems in chloroform and in dioxan solutions, using Job's method of continuous variations.[7] Optical-density values for these plots have been obtained, first by extrapolating the optical density–time plots

FIG. 1.

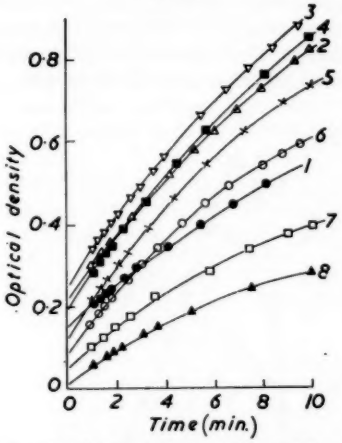


FIG. 2.

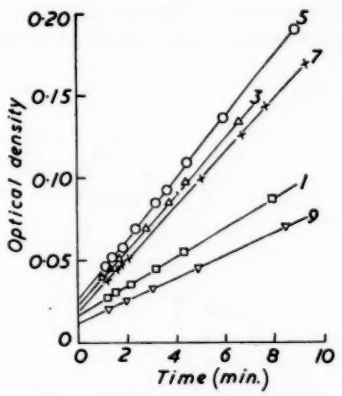


FIG. 1. *Development of absorption at* 480 mμ *for solutions of trinitrobenzene* (TNB)*–diethylamine in chloroform.*

Curve	1	2	3	4	5	6	7	8
[TNB] (M)	0·022	0·044	0·066	0·088	0·110	0·132	0·154	0·176
[Amine] (M)	0·198	0·176	0·154	0·132	0·110	0·088	0·066	0·044

FIG. 2. *Development of absorption at* 480 mμ *for solutions of trinitrobenzene* (TNB)*–di-s-butylamine in chloroform (for clarity only half the continuous-variation solutions are shown).*

Curve	1	3	5	7	9
[TNB] (M)	0·023	0·069	0·115	0·161	0·207
[Amine] (M)	0·207	0·161	0·115	0·069	0·023

to zero time to give the molar ratio of the instantaneous interaction product and, secondly from optical densities of the solutions at a time when further colour development is very slow relatively to the initial rate. The results are summarised in Table 2.

TABLE 2. *Molar ratios of amine : trinitrobenzene obtained from Job plots* (i) *at time of mixing,* (ii) *at "equilibrium."*

Amine	Solvent	(i)	(ii)	Amine	Solvent	(i)	(ii)
NH_3	$CHCl_3$	*a*	*a*	$NHEt_2$	$CHCl_3$	3 : 1	3 : 1
NH_2Me	,,	3 : 1	3 : 1	,,	Dioxan	3 : 1	3 : 1
,,	Dioxan	3 : 1	3 : 1	$NHBu^s_2$	$CHCl_3$	*a*	1 : 1
NH_2Et	$CHCl_3$	3 : 1	3 : 1	NMe_3	,,	*a*	1 : 1
$NHMe_2$	,,	3 : 1	3 : 1	NH_2Me [b]	,,	*a*	1 : 1
,,	Dioxan	3 : 1	3 : 1				

[a] No measurable additional absorption above 440 mμ in solutions of total concentration [amine] + [TNB] ~0·25M. [b] *m*-Dinitrobenzene in place of trinitrobenzene.

Ainscough and Caldin [8] have shown that there are two colour-producing reactions when sodium ethoxide is added to 2,4,6-trinitroanisole: a "fast" reaction, the product of which

[5] Foster, Hammick, and Wardley, *J.*, 1953, 3817.
[6] Ross and Labes, *J. Org. Chem.*, 1956, **21**, 1049.
[7] Job, *Compt. rend.*, 1925, **180**, 928; *Ann. Chim.*, 1928, **9**, 113; 1936, **6**, 97.
[8] Ainscough and Caldin, *J.*, 1956, 2528.

XUM

is probably a charge-transfer complex, and a " slow " reaction probably involving an addition compound as described by Meisenheimer.[9] There is evidence that a product of this latter type is also formed on addition of sodium ethoxide to trinitrobenzene.[10] It is possible that these two processes occur in the systems we are studying. The optical density at zero time would then be accounted for by the fast formation of the charge-transfer complex, which is followed by the slow interaction.

Further evidence for initial complex formation is the intensification of colour shown by chloroform solutions when cooled in ethanol–solid carbon dioxide. This is to be expected because of the increased degree of association at lower temperatures. Ham,[11] for example, calculates the association constant of pyridine–iodine to be $3{\cdot}1 \times 10^{19}$ at 77° K compared with 1250 at 298° K. The effect is large for complexes of trinitrobenzene with the sterically " small " amines: methylamine, ethylamine, dimethylamine, and diethylamine. With

FIG. 3.

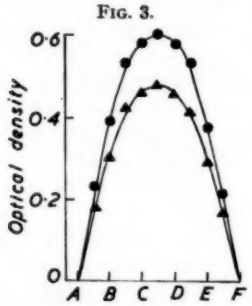


FIG. 4.

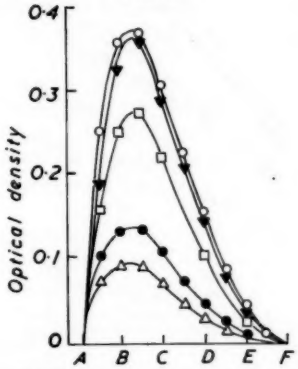


FIG. 3. *Continuous variation plot*: m-*dinitrobenzene* (DNB)–*methylamine in chloroform two days after mixing*: ● 450 mμ, ▲ 460 mμ.

	A	*B*	*C*	*D*	*E*	*F*
[DNB] (M)	0·000	0·030	0·059	0·089	0·119	0·148
[Amine] (M)	0·148	0·119	0·089	0·059	0·030	0·000

FIG. 4. *Continuous variation plot*: *trinitrobenzene* (TNB)–*methylamine in chloroform* 20 *min. after mixing*: ○ 450 mμ, ▼ 490 mμ, □ 520 mμ, ● 540 mμ, △ 570 mμ.

	A	*B*	*C*	*D*	*E*	*F*
[TNB] (M)	0·000	0·044	0·088	0·132	0·175	0·219
[Amine] (M)	0·219	0·175	0·132	0·088	0·044	0·000

these amines, estimations by eye of colour intensity of the appropriate cooled solutions confirm a 3 : 1 stoicheiometry of the initial complexes. This temperature effect is only slight in the systems with the " bulky " amines di-s-butylamine and trimethylamine, and also in the system *m*-dinitrobenzene–methylamine. With ammonia no colour appear until the solution has solidified, whereafter an intense red is observed. In the last systems, initial complex formation appears to be very slight or absent.

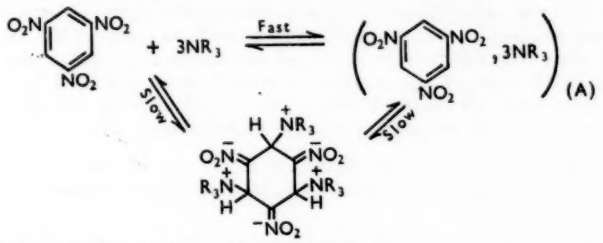
The second process, because of its slowness, may involve covalent-bond formation. Lewis and Seaborg [12] had previously assumed that there is attachment of only one amine molecule to the trinitrobenzene molecule and considered three possible mechanisms of interaction: (1) direct loss of hydrogen from trinitrobenzene, (2) direct addition of the base to one of the ring-carbon atoms that is not attached to a nitro-group, and (3) attachment of the base to one of the nitrogen atoms. The first is unlikely from general principles and

[9] Meisenheimer, *Annalen*, 1902, **323**, 205.
[10] Foster, *Nature*, 1959, **183**, 1042.
[11] Ham, *J. Amer. Chem. Soc.*, 1954, **76**, 3875.
[12] Lewis and Seaborg, *ibid.*, 1940, **62**, 3529.

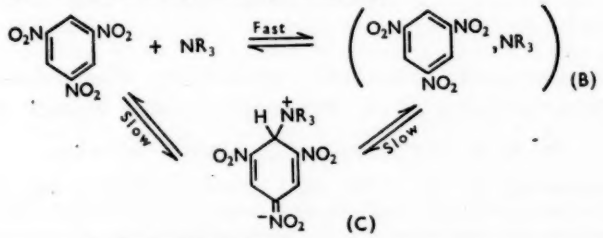
from the work of Ketelaar, Bier, and Vlaar [13] who showed that there is no exchange between trinitrobenzene and heavy water in the presence of sodium hydroxide. If (3) were the mechanism, then by analogy with the formation of a 3 : 1 methylamine–trinitrobenzene compound we might expect each of the three dinitrobenzenes to give 2 : 1 adducts. In fact there is no observable interaction between *o*- or *p*-dinitrobenzene and aliphatic amines at room temperature. With *m*-dinitrobenzene a colour develops very slowly. From measurements of optical density made two days after mixing, a continuous-variation plot indicates a 1 : 1 interaction (Fig. 3). If, after this time, the amine and solvent are removed *in vacuo*, *m*-dinitrobenzene is recovered quantitatively. The most likely of Lewis and Seabourg's suggestions seems therefore to be (2) which corresponds to the Meisenheimer type of addition, except that in cases where it is sterically possible we suggest that three molecules of amine add to the trinitrobenzene. This is feasible as here the nucleophile is uncharged species; in contradistinction the attack on trinitrobenzene by the methoxide ion results in an anion which repels the attack of a second and a third methoxide ion.

It is therefore suggested that there may be immediate formation of a charge-transfer complex and a concurrent or consecutive addition reaction:

(a) for " small " amines, $NR_3 = NH_2Me$, NH_2Et, $NHMe_2$, $NltEt_2$



(b) for " bulky " amines, $NR_3 = NMe_3$, $NH_2Bu^s{}_2$:



A: Charge-transfer complex.
B: Charge-transfer complex weak (if present at all).
C: Or other canonical structures.

The supposition that the amine nucleophile will only attack a carbon atom activated by two nitro-groups *ortho* to that position would also account for the reaction of methylamine with *m*-dinitrobenzene to yield a 1 : 1 adduct and the absence of reaction with *o*- and *p*-dinitrobenzene.

Absence of free ions in these solutions is indicated by their low electrical conductivity; for example, a chloroform solution 0·2M with respect to both methylamine and trinitrobenzene has a conductivity of $\sim 10^{-6}$ ohm^{-1} cm.$^{-1}$.

Experimental

Materials.—1,3,5-Trinitrobenzene, recrystallised four times from ethanol, then twice from carbon tetrachloride, had m. p. 123°. *m*-Dinitrobenzene, similarly purified, had m. p. 90°.

[13] Ketelaar, Bier, and Vlaar, *Rec. Trav. chim.*, 1954, **73**, 37.

Methyl-, ethyl-, dimethyl-, and diethyl-amine hydrochloride were recrystallised twice from absolute ethanol, concentrated aqueous solutions of these salts were dropped on solid sodium hydroxide, and the gaseous free bases, dried through 2′ columns of soda-lime, were absorbed in the appropriate solvent. Trimethylamine solutions were similarly obtained from the hydriodide twice recrystallised from methanol. Other amines were fractionally distilled from solid potassium hydroxide. " AnalaR " chloroform was washed eight times with equal volumes of water to remove ethanol, stored over calcium chloride, then refluxed for 2 hr. over phosphoric oxide and distilled. Dioxan was purified by Vogel's method.[14]

Analyses.—Job's continuous-variation method [7] has been used to determine the molar ratios. The formation of the product of an interaction between trinitrobenzene (A) and an amine (B) may be represented: $A + nB \rightleftharpoons AB_n$. To determine n, solutions of A and B of the same molar concentration are mixed in varying proportions by the additions of x ml. of a solution of B to $(10 - x)$ ml. of a solution of A, and a suitable property of the resulting solutions is measured. The difference between the value found and the corresponding value of the property calculated for no reaction is plotted against composition. The resulting curve will show a maximum (or minimum) at the value of x such that $n = x/(1 - x)$.

Such plots (Figs. 3 and 4) have been constructed by measuring the optical density at given wavelengths; first, from values extrapolated against time (Figs. 1 and 2) to give the molar ratio for the instantaneous interaction product and, secondly, from optical densities of solutions which have come to equilibrium or in which the rate of colour development is relatively very slow. The only purpose of the plots of optical density against time has been to determine the values at the time of mixing. No attempt has been made to interpret the kinetic data.

Solutions of nitro-compounds were made up gravimetrically; the amine solutions were standardised by acidimetry. From primary solutions sets of solutions for the continuous-variation plots were made up volumetrically. The optical densities were measured in 1 cm. stoppered fused silica cells at 20° with an Optica grating spectrophotometer.

The author is grateful to Dr. D. Ll. Hammick, F.R.S., for his interest in this work which was carried out mainly during the tenure of an Edward A. Deeds Fellowship of the University of St. Andrews.

Queen's College (University of St. Andrews), Dundee. [*Received, May 22nd,* 1959.]

[14] Vogel, " A Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 175.

---

707. *Ipecacuanha Alkaloids. Part IV.* The Relative and Absolute Stereochemistry of the Benzoquinolizidine System of Emetine.*

By A. R. Battersby and S. Garratt (née Cox).

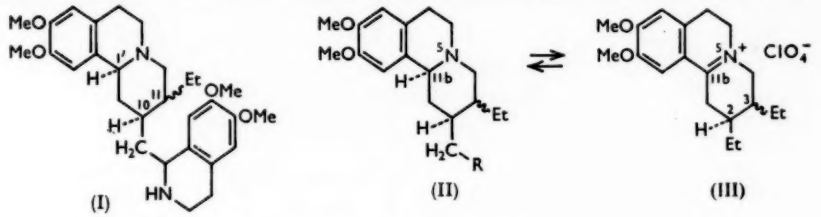
Protoemetine (II; R = CHO), which is known to have the same stereochemistry as emetine, has been reduced to deoxyprotoemetine (II; R = Me). The two possible diastereoisomers of (II; R = Me) having the ethyl groups respectively *cis* and *trans* have been synthesised stereospecifically. By comparison of these products with deoxyprotoemetine, the latter has been proved to be the *trans*-base. Thus protoemetine has the stereochemistry (V) and it follows that emetine has the structure (XXII; R = Me). This leads to a knowledge of the stereochemistry of the minor alkaloids of Ipecacuanha.

In Part III,* it was established that the tricyclic system of emetine (I) has the stereochemistry shown or that it has the mirror image form of this structure. Recently we have proved [1] that the *absolute* stereochemistry drawn for emetine (I) is in fact the true one; thus, only the relative configuration of the 11-ethyl group remains to be determined. The present paper describes the use of protoemetine (II; R = CHO), the aldehydic Ipecacuanha alkaloid,[2] to provide a solution to this problem. Protoemetine is an ideal starting point

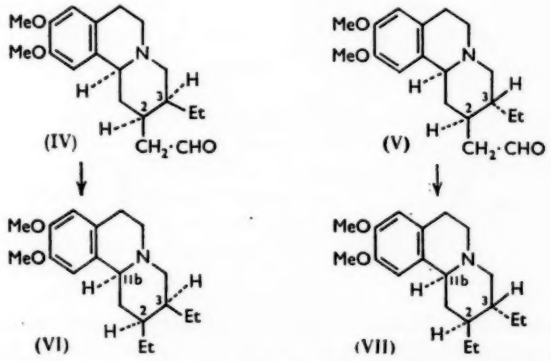
* Part III, *J.*, 1959, 2704.

[1] Battersby and Garratt, *Proc. Chem. Soc.*, 1959, 86.
[2] Battersby, Davidson, and Harper, *J.*, 1959, 1744.

since Battersby and Harper have converted it into emetine;[3] the two alkaloids therefore have the same relative and absolute stereochemistry. It follows that protoemetine must have the structure (IV) or (V) depending upon whether there is a *cis*- or a *trans*-arrangement, respectively, about the 2,3-bond corresponding to the 10,11-bond of emetine. A decision



(I) (II) (III)



(IV) (V) (VI) (VII)

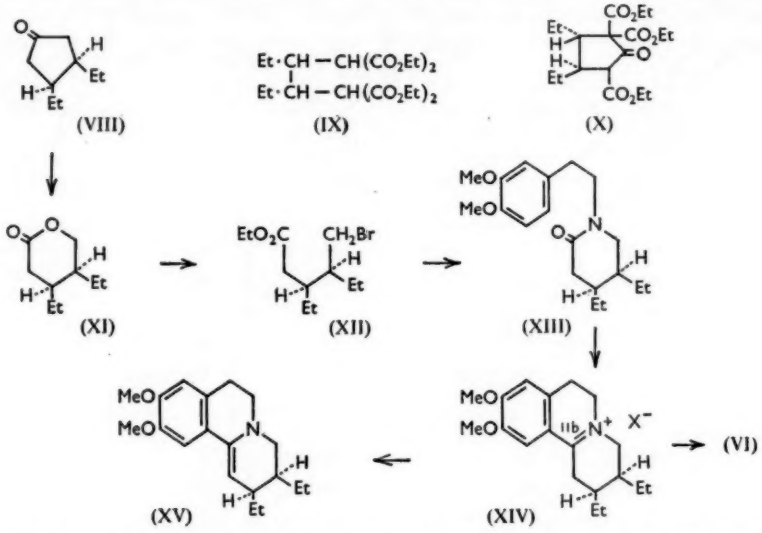
between the two possibilities was reached by reduction of protoemetine to deoxyprotoemetine which must have the structure (VI) or (VII); stereospecific syntheses of these two bases then provided the necessary materials for comparison with deoxyprotoemetine. For simplicity, only one enantiomer of each synthetic product is drawn in this paper, although the products are in fact all racemic.

Clemmensen reduction of protoemetine (II; R = CHO) gave a mixture from which only dihydroprotoemetine (II; R = CH_2·OH) could be isolated; we therefore turned to Wolff–Kishner reduction (Huang-Minlon modification [4]). Gates and Tschudi [5] found in one case that this modification can be used successfully at much lower temperatures than those (~200°) originally suggested, and Barton, Ives, and Thomas [6] showed that the reducing power is greatly improved when all the components in the reaction mixture are completely anhydrous. Combining these observations, we reduced protoemetine semicarbazone at 155° in anhydrous ethylene glycol with anhydrous hydrazine and alkali. Deoxyprotoemetine (II; R = Me) was isolated in 87% yield as its crystalline perchlorate.

The possibility that base-catalysed inversion of one or more asymmetric centres could have occurred in the above reduction was eliminated by subjecting emetine (I) to the Wolff–Kishner conditions. It was found that 94% of the non-phenolic basic material isolated from this reaction was unchanged emetine and the identity of the recovered alkaloid was established by rigorous comparison with the natural base and by conversion into the crystalline *N*-benzoylemetine. There is thus no doubt that deoxyprotoemetine (II; R = Me), which expanded becomes structure (VI) or (VII), has the same stereochemistry as protoemetine and emetine.

[3] Battersby and Harper, *J.*, 1959, 1748.
[4] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[5] Gates and Tschudi, *ibid.*, 1956, **78**, 1380.
[6] Barton, Ives, and Thomas, *J.*, 1955, 2056.

Dehydrogenation of deoxyprotoemetine (II; R = Me) with mercuric acetate [7] gave dehydrodeoxyprotoemetine perchlorate (III) which had the expected ultraviolet absorption. Catalytic hydrogenation of this salt gave the starting material (II; R = Me) in high yield; hydrogen is therefore added at position 11b *cis* with respect to the 2-hydrogen atom.



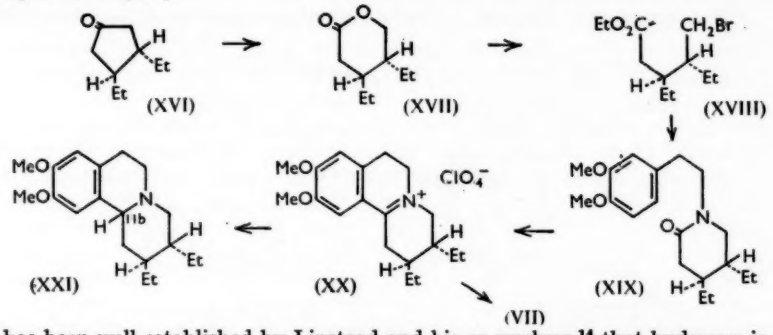
This observation was of considerable importance in plans for a stereospecific synthesis of emetine [8] and it is discussed further below.

The synthetic route to the diethyl bases (VI) and (VII) was suggested by that used for the controlled synthesis of alloyohimbane [9] and yohimbane [10] and it will be illustrated for the synthesis of the *cis*-base (VI). *cis*-3,4-Diethylcyclopentanone (VIII) had been prepared by Koelsch and Stratton [11] who firmly established its stereochemistry. We followed their method which has an interest aside from our main theme since it involves at one stage the treatment of a mixture of (±)- and *meso*-diethyl αδ-diethoxycarbonyl-βγ-diethyladipate (IX) under weakly basic conditions. The resultant formation of triethyl 4,5-diethyl-2-oxocyclopentane-1,1,3-tricarboxylate (X) from the (±)-ester whereas the *meso*-ester is largely unchanged can now be interpreted as conformational control of the 1,2-*cis*-cyclisation; [12] one can compare the case of acetone condensing at a slower rate with *meso*- than with (±)-dihydrobenzoin.[13]

The action of perbenzoic acid on the *cis*-diethylcyclopentanone (VIII) yielded the lactone (XI) of *erythro*-βγ-diethyl-δ-hydroxyvaleric acid which was converted into ethyl *erythro*-δ-bromo-βγ-diethylvalerate (XII) by hydrogen bromide in ethanol. Simple distillation did not separate the bromo-ester (XII) from unchanged lactone, but the bromine content of our product showed that it contained about 80% of the required bromide. This reacted readily with 3,4-dimethoxyphenethylamine in the presence of potassium carbonate to give the 2-piperidone (XIII); the structure is assigned on the basis of the analysis of this neutral product and of its infrared spectrum which showed a strong band at 1640 cm.$^{-1}$ (N·CO), but no OH or NH bands. The piperidone was cyclised by

[7] Leonard, Hay, Fulmer, and Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 439.
[8] Battersby and Turner, *Chem. and Ind.*, 1958, 1324.
[9] Stork and Hill, *J. Amer. Chem. Soc.*, 1954, **76**, 949.
[10] van Tamelen and Shamma, *ibid.*, p. 950.
[11] Koelsch and Stratton, *ibid.*, 1944, **66**, 1881.
[12] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.
[13] Hermans, *Z. phys. Chem.*, 1924, **113**, 337.

phosphorus oxychloride in boiling toluene, and the product was isolated as the crystalline iodide (XIV; $X^- = I^-$) or perchlorate (XIV; $X^- = ClO_4^-$). The latter salt showed the ultraviolet spectrum characteristic of 3,4-dihydroisoquinolinium quaternary salts and the spectrum was altered in the expected way on addition of alkali owing to the formation of the anhydro-base (XV).



It has been well established by Linstead and his co-workers [14] that hydrogen is transferred from a catalyst to the least hindered side of an unsaturated molecule. We can therefore assign the structure (VI), which is the required (±)-*cis*-diethyl base, to the product formed in 74% yield by catalytic hydrogenation of the perchlorate (XIV; $X^- = ClO_4^-$). Reduction of the latter salt with sodium borohydride also gave the same base (VI).

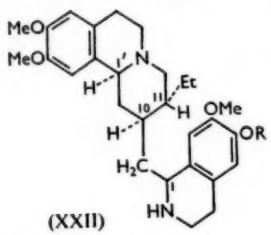
For the synthesis of the corresponding (±)-*trans*-diethyl base (VII), *trans*-3,4-diethylcyclopentanone (XVI) was regenerated by acid hydrolysis from its pure semicarbazone which is readily available by Koelsch and Stratton's method.[11] The remaining stages to the quaternary salt (XX), as shown in the charts, follow those used in the *cis*-series; the *threo*-bromo-ester (XVIII) has recently been prepared independently [15] for closely related studies in the indole series. In contrast to the *cis*-isomer (XIV), the two sides of the *trans*-molecule (XX) are about equally open to approach by the catalyst, so that one cannot predict the result of catalytic hydrogenation on steric grounds. In practice, the hydrogenation and also reduction with sodium borohydride gave the same isomer in good yield, and the infrared spectrum of this product, determined in solution, was identical with that of the reduction product from protoemetine known to have the structure (VI) or (VII). The infrared spectrum of the (±)*cis*-base (VI) was clearly different from that of the *trans*-isomer. These results establish conclusively that the reduction product from protoemetine is the *trans*-base (VII); it follows that protoemetine has the structure (V) and emetine the structure (XXII; R = Me).

Further support was obtained by showing that the infrared spectrum of the salt (III), obtained by mercuric acetate dehydrogenation of deoxyprotoemetine (II; R = Me), was identical with that of the synthetic *trans*-salt (XX); both spectra were determined in solution. The spectrum given by the synthetic *cis*-salt (XIV; $X = ClO_4^-$) was significantly different. These results also establish the illustrated position of the double bond in the salt (III) which we assigned above on the basis of ultraviolet absorption.

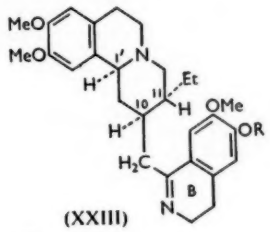
The foregoing evidence shows that hydrogenation of the *trans*-salt (XX) yields the more thermodynamically stable base (VII) rather than the other possible product (XXI). This also occurs when indole derivatives closely related to our materials are hydrogenated; thus 3-dehydroyohimbane chloride yields mainly yohimbane [10] and there are other similar cases.[15,16] It seems probable that thermodynamic control is a general phenomenon for this type of hydrogenation.

[14] Davis, Doering, Levine, and Linstead, *J.*, 1950, **1423**; Linstead and Whetstone, *ibid.*, p. 1428 and refs. therein.
[15] van Tamelen, Aldrich, and Katz, *J. Amer. Chem. Soc.*, 1957, **79**, 6426.
[16] Wenkert and Roychaudhuri, *J. Org. Chem.*, 1956, **21**, 1315.

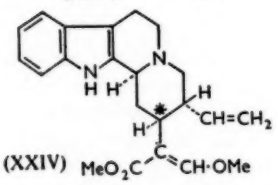
Reduction of the *trans*-salt (XX) by zinc in acetic acid gave the base (VII) together with an isomeric base which was separated as the sparingly soluble picrate. The latter base was shown to be tertiary by its failure to react with acetic anhydride and it was dehydrogenated by mercuric acetate in acetic acid with regeneration of the starting material (XX); the new isomer must therefore have the structure and stereochemistry (XXI). There was a clear difference between the infrared spectra of the bases (VII) and



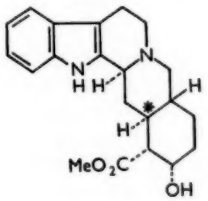
(XXII)



(XXIII)



(XXIV)



(XXV)

(XXI) when examined as films, and both showed the absorption at 2750 ± 10 cm.$^{-1}$ characteristic of the *trans*-conformation of the quinolizidine system.[17] In this conformation the base (XXI) has two axial ethyl groups and attempts were made to convert it into the thermodynamically more stable base (VII) by using potassium t-butoxide in boiling t-butyl alcohol for 20 hr. These conditions did not cause fission of the weakly activated $C_{(11b)}$–H bond which is necessary for the desired conversion, and the starting material was recovered unchanged; similarly the base (VII) was unaffected under these conditions. More drastic treatment of the bases for 13 hr. with boiling ethylene glycol in which sodium had been dissolved caused general breakdown. Attempted reduction of the salt (XX) with sodium in liquid ammonia, both with and without ammonium chloride in the solvent, gave starting material as the only isolable solid. However, in agreement with van Tamelen *et al.*,[18] reduction of the *trans*-salt (XX) with sodium and ethanol gave a mixture yielding the base which had been prepared earlier from the salt (XX) by catalytic hydrogenation. This result supports our earlier assignment of the stereochemistry (VII) to this base since reduction with sodium and alcohol is known [19] to give the thermodynamically more stable product. The base (XXI) must be formed at most in small amount by the sodium–ethanol reduction as we were unable to isolate it from the reaction mixture as the picrate despite the ease of crystallisation and sparing solubility of this salt.

All the foregoing evidence and that given in Part III [20] interlocks, and the stereochemistry (XXII; R = Me) for emetine is established. The minor alkaloids of Ipecacuanha have been directly related [21,20] with emetine by chemical means so that the stereochemistries of cephaeline (XXII; R = H), *O*-methylpsychotrine (XXIII; R = Me),

[17] Bohlmann, *Angew. Chem.*, 1957, **69**, 641; *Chem. Ber.*, 1958, **91**, 2157; Wenkert and Roychaudhuri, *J. Amer. Chem. Soc.*, 1956, **78**, 6417.
[18] van Tamelen, Aldrich, and Hester, *J. Amer. Chem. Soc.*, 1957, **79**, 4817; cf. van Tamelen and Hester, *ibid.*, 1959, **81**, 507.
[19] Barton and Robinson, *J.*, 1954, 3045 and refs. therein.
[20] Battersby, Binks, and Davison, *J.*, 1959, 2704.
[21] Reviewed by Janot, " The Alkaloids," ed. Manske and Holmes, Academic Press, Inc., New York, 1953, Vol. III, p. 363;

psychotrine (XXIII; R = H), and emetamine [22] (XXIII; R = Me with ring B aromatised) are now known.

It should be emphasised that the absolute configuration at position 10 of emetine (XXII; R = Me) is the same as that at the corresponding carbon atom in all those indole alkaloids which are thought to be biosynthesised from tryptophan and phenylalanine or their equivalents.[23,24] This carbon atom is marked * in corynantheine [15,24] (XXIV) and yohimbine [25] (XXV) which are given as examples. We have discussed elsewhere [1] the considerable biogenetic interest of this correlation between the Ipecacuanha and indole alkaloids.

After our publication of the preliminary account of most of the foregoing work,[26] van Tamelen, Aldrich, and Hester reported briefly [18] the synthesis of the *trans*-base (VII). By correlating it with an intermediate used in the Russian synthesis of emetine,[27] and by using the determination from this laboratory of the absolute configuration at position 1 of emetine [28] in conjunction with further optical studies, they also derived the stereochemistry (XXII) for emetine, in agreement with our work. The *trans*-arrangement at positions 10 and 11 of emetine was subsequently given further support by Brossi *et al.*[29] using a different approach, and recently [31] Ban and his co-workers have published results which are in agreement with ours concerning the relative and absolute stereochemistry at position 1'.

Experimental

For general directions see Part I.[2]

Clemmensen Reduction of Protoemetine (V).—An ethereal solution of protoemetine, freshly recovered from the perchlorate monohydrate (0·15 g.), was shaken with 6N-hydrochloric acid (15 ml.), and the acidic solution was heated with amalgamated granular zinc (1·1 g.) for 0·5 hr. on the water-bath, kept at room temperature for 24 hr., heated again on the water-bath for 24 hr., decanted from the excess of zinc, and evaporated to dryness. The residue was dissolved in water and made strongly alkaline with sodium hydroxide. Ether-extraction yielded a gum (0·1 g.) which was converted into the perchlorate in aqueous ethanol; a mixture of partly crystalline lumps and fine crystals was precipitated. The latter were separated by hand and after recrystallisation from water had m. p. 198—199°, unchanged in admixture with dihydroprotoemetine perchlorate [3] (as II; R = CH_2·OH); the two samples of perchlorate had identical infrared spectra (in Nujol).

Wolff–Kishner Reduction of Protoemetine (V).—Anhydrous protoemetine semicarbazone [3] (425 mg.) was added to a warm (60°) solution of potassium hydroxide (2·5 g.) and anhydrous hydrazine (5 ml.) in dry ethylene glycol (10 ml.). The mixture was protected against moisture and was heated at 155° for 5 hr. After the cooled solution had been diluted with water (50 ml.), it was extracted thrice with ether, each ether layer being washed twice with water. Evaporation of the dried ethereal solution left a gum (315 mg.) which, in aqueous ethanol, was converted into the perchlorate. *Deoxyprotoemetine* (VII) *perchlorate* separated as prisms (398 mg., 87%), m. p. 105—107° to a resin which flowed at 176—177°, unchanged by recrystallisation from aqueous ethanol (Found, in sample dried first at 78° and then to constant weight at 100°: C, 56·6; H, 7·7; N, 3·8. $C_{19}H_{30}O_6NCl$ requires C, 56·5; H, 7·5; N, 3·5%), $[\alpha]_D^{20}$ −41·0° (*c* 5·25 in aqueous ethanol made from 70 ml. of ethanol and 5 ml. of water).

[22] Battersby, "Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds," The Chemical Society, London, 1955, p. 36 and refs. therein.
[23] Woodward, *Nature*, 1948, **162**, 155; Robinson, *ibid.*, 524; Saxton, *Quart. Reviews*, 1956, **10**, 108; Bose, *Chem. and Ind.*, 1958, 1690.
[24] Wenkert and Bringi, *J. Amer. Chem. Soc.*, 1958, **80**, 3484; 1959, **81**, 1474.
[25] Klyne, *Chem. and Ind.*, 1953, 1032.
[26] Battersby and Cox, *Chem. and Ind.*, 1957, 983.
[27] Evstigneeva, Livshits, Bainova, Zakharkin, and Preobrashenski, *J. Gen. Chem.* (*U.S.S.R.*), 1952, **22**, 1467.
[28] Battersby, Binks, Davidson, Davidson, and Edwards, *Chem. and Ind.*, 1957, 982.
[29] Brossi, Cohen, Osbond, Plattner, Schnider, and Wickens, *ibid.*, 1958, 491; cf. Osbond, *ibid.*, 1959, 257.
[30] Carr and Pyman, *J.*, 1914, **105**, 1591.
[31] Ban, Terashima, and Yonemitsu, *Chem. and Ind.*, 1959, 568, 569.

Deoxyprotoemetine base was recovered into ether as usual and was distilled at 120° (bath)/0·05 mm. for determination of its infrared spectrum (in CS_2) which showed $\nu_{max.}$ 2745 cm.$^{-1}$, no OH or C=O bands. The distilled base subsequently crystallised and had m. p. 58—59°, but the amount available was insufficient to allow recrystallisation; it had $[\alpha]_D^{20}$ −75·3° (*c* 1·13 in ethanol).

Treatment of Emetine under Wolff–Kishner Conditions.—Emetine, freshly recovered from the pure hydrochloride, had $[\alpha]_D^{20}$ −49·2° ± 1° (*c* 3·56 in chloroform) (lit.,[30] −50°). This base (0·66 g.) was heated as was protoemetine above with potassium hydroxide (3·5 g.) and anhydrous hydrazine (3·5 ml.) in dry ethylene glycol (7 ml.). The non-phenolic bases (0·59 g.), recovered as above, were dissolved in a slight excess of hydrochloric acid, and the solution was diluted to 40 ml. After the addition of ammonium bromide (1 g.), emetine hydrobromide crystallised (0·799 g., containing 7·1% of water), m. p. 248—256° unchanged on admixture with authentic emetine hydrobromide of the same m. p. Part of the base recovered from the above hydrobromide had $[\alpha]_D^{18}$ −46·5° ± 1° (*c* 3·55 in chloroform) and its infrared spectrum (in $CHCl_3$) was superimposable on that of authentic emetine base; the remaining base was converted by Carr and Pyman's method [30] into *N*-benzoylemetine (62% yield), m. p. 181·5—182·5° unchanged on admixture with authentic *N*-benzoylemetine of the same m. p. The preparation of the latter was carried out on the same scale as the preceding benzoylation (60% yield). The two samples of *N*-benzoylemetine had identical infrared spectra (in Nujol).

Mercuric Acetate Oxidation of Deoxyprotoemetine (VII).—The base (VII), recovered from its perchlorate (181 mg.), was dissolved in warm 15% aqueous acetic acid (2 ml.) and added to a warm solution of mercuric acetate (0·41 g.) and potassium acetate (24 mg.) in 15% aqueous acetic acid (1 ml.). After this solution had been heated under reflux for 1·5 hr., it was cooled and filtered, and the pad was washed with water and ethanol. The filtrate was boiled and then allowed to cool during 20 min. under a pressure of hydrogen sulphide. 2N-Hydrochloric acid was added, the solution was boiled, and the treatment with hydrogen sulphide was repeated. The sulphides were filtered off (" Filtercel ") and washed with water and ethanol, and the filtrate was concentrated to 2 ml. Addition of 60% perchloric acid (5 drops) caused separation of *dehydrodeoxyprotoemetine perchlorate* (XX) which was recrystallised from aqueous ethanol and gave prisms (149 mg.), m. p. 165—166° (Found: C, 57·1; H, 7·4. $C_{19}H_{28}O_6NCl$ requires C, 56·8; H, 7·0%), $[\alpha]_D^{20}$ +79° (*c* 1·22 in aqueous ethanol made from 70 ml. ethanol and 5 ml. water), $\lambda_{max.}$ 250, 310, 355, $\lambda_{min.}$ 240, 275, 330 mμ (log ε 4·33, 3·97, 4·01, 4·28, 3·33, 3·77 respectively in EtOH), changed to $\lambda_{max.}$ 296, $\lambda_{min.}$ 280 mμ (log ε 3·81, 3·78 respectively) when the solution was made alkaline with sodium hydroxide; it had $\nu_{max.}$ 1647 cm.$^{-1}$ ($C{=}N^+$), no band in 2750 ± 10 cm.$^{-1}$ region (in $CHCl_3$).

Hydrogenation of Dehydrodeoxyprotoemetine Perchlorate (XX).—A solution of this salt (80 mg.) in 4 : 1 ethanol–water (12·5 ml.) was shaken with hydrogen and platinum at 18°/747 mm.; uptake (1·01 mol.) ceased after 17 min. The catalyst was filtered off and the solution concentrated to 2 ml. Deoxyprotoemetine perchlorate (VII) crystallised (67 mg.), having m. p. behaviour as recorded above, unchanged on admixture with authentic material. The infrared spectrum (in Nujol) and the *X*-ray powder photograph were identical with those of deoxyprotoemetine perchlorate (VII).

Lactone (XI) *of* erythro-β*γ-Diethyl-*δ*-hydroxyvaleric Acid.—cis*-3,4-Diethylcyclopentanone (2·78 g.) was added to a solution of perbenzoic acid (3·86 g.) in moist chloroform (75 ml.) and after 7 days at room temperature the solution was shown by titration of an aliquot part to contain 0·02 g. of perbenzoic acid. Ether (200 ml.) was then added and this solution was shaken with 5% sodium carbonate solution (3 × 20 ml.). Evaporation of the organic layer left an oil which in ethanol (100 ml.) was treated with N-sodium hydroxide (66 ml.) and water (100 ml.). This solution was extracted with ether (3 × 100 ml.), and the aqueous layer and washings were acidified to Congo Red with hydrochloric acid and re-extracted with ether (3 × 150 ml.). Evaporation of the dried ethereal solution and distillation of the residue gave the crude lactone (XI) (2·1 g.), b. p. 146—148°/20 mm. The ultraviolet spectrum of this product suggested strongly that it was contaminated with benzoic acid and for purification it was fractionated on a column of silica gel. Elution with benzene–chloroform (1 : 1) yielded the best sample of the cis-*lactone* (XI), though still not completely pure, which was redistilled for analysis (Found: C, 68·7; H, 9·6. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%).

Ethyl erythro-β*γ-Diethyl-*δ*-bromovalerate* (XII).—A solution of the foregoing crude lactone (4·66 g.) in absolute ethanol (20 ml.) was saturated at 0° with dry hydrogen bromide and then

kept at 5° for 19 hr. The mixture was poured on ice and water, and the products were extracted quickly into ether. After the ethereal solution had been washed with 15% potassium carbonate solution (20 ml.) and water, it was dried and evaporated. The residue yielded a fraction (5·5 g.), b. p. 133—134°/13 mm., containing the bromo-ester (XII) (Found: Br, 24·8%; corresponding to 82% of the bromo-ester).

cis-1-(3,4-*Dimethoxyphenethyl*)-4,5-*diethyl*-2-*oxopiperidine* (XIII).—The foregoing crude bromo-ester (3·52 g.), 3,4-dimethoxyphenethylamine (3·22 g.), potassium carbonate (1·63 g.), potassium iodide (1 crystal), and butan-1-ol (10 ml.) were heated together at 80° under nitrogen for 4 hr. and then under reflux for a further 42 hr. After addition of water to the cooled solution, it was extracted thrice with ethyl acetate, and the combined organic layers were washed with 0·5N-hydrochloric acid (2 × 20 ml.) and water. Evaporation of the dried ethyl acetate solution left the neutral products which were distilled at 5 × 10^{-5} mm. After a small fraction up to 130° (bath), the *oxopiperidine* (XIII) distilled at 140—190° (bath), mainly at 170°. This product is sufficiently pure for use in the next stage, but part was purified on a silica gel column, with chloroform–benzene (1 : 1) for elution. Redistillation of the eluate in a short-path still gave the pure oxopiperidine (XIII) (Found: C, 71·9; H, 9·3; N, 4·0. $C_{19}H_{29}O_3N$ requires C, 71·45; H, 9·15; N, 4·4%).

cis-5,11b-*Dehydro*-2,3-*diethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Iodide* (XIV; $X^- = I^-$) *and Perchlorate* (XIV; $X^- = ClO_4^-$).—Freshly distilled phosphoryl chloride (20 ml.) was heated under reflux for 1 hr. in anhydrous toluene (50 ml.) containing the foregoing oxopiperidine (2 g.). The cooled solution was poured on ice, and the separated toluene layer was extracted twice with dilute hydrochloric acid. The combined aqueous solution was extracted thrice with ether, made strongly alkaline with potassium hydroxide, and re-extracted with ether, each extract being washed with water. The combined ethereal solution was then extracted with 0·5N-hydrochloric acid (20 + 10 ml.), and concentrated potassium iodide solution was added to the combined acidic extracts. Recrystallisation of the precipitate from acetone–ether gave the *quinolizinium iodide* (XIV; $X^- = I^-$) (1·27 g.), m. p. 159—160° (Found: C, 52·8; H, 6·5; N, 3·4. $C_{19}H_{28}O_2NI$ requires C, 53·2; H, 6·6; N, 3·3%).

The iodide (0·1 g.) was treated with potassium hydroxide solution, and the iso-base (XV) was extracted into ether and recovered from it as a gum by evaporation at *ca.* 20°. A solution of this gum in ethanol was treated with 60% perchloric acid (5 drops) to yield the *quinolizinium perchlorate* (XIV; $X^- = ClO_4^-$) (88 mg.) which, recrystallised from aqueous ethanol, had m. p. 171—172° (Found: C, 56·9; H, 7·1. $C_{19}H_{28}O_6NCl$ requires C, 56·8; H, 7·0%), $\nu_{max.}$ (in $CHCl_3$) 1647 $cm.^{-1}$ ($C{=}N^+$).

cis-2,3-*Diethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizine* (VI).—(a) *Catalytic reduction.* The foregoing perchlorate (338 mg.) was hydrogenated (uptake 1·02 mol.) and worked up as described for the reduction of dehydrodeoxyprotoemetine perchlorate above, to give a crystalline perchlorate (294 mg.). This was recrystallised from aqueous ethanol to yield the *quinolizine perchlorate* (as VI) as needles (250 mg., 74%), m. p. 198—199° (Found: C, 56·8; H, 7·5; N, 3·9. $C_{19}H_{30}O_6NCl$ requires C, 56·5; H, 7·5; N, 3·5%), $\lambda_{max.}$ 232·5, 283·5, $\lambda_{min.}$ 219, 265 mμ (log ε 4·01, 3·54, 3·91, 3·17 respectively) in EtOH.

For infrared comparison with deoxyprotoemetine, the base was recovered from the pure perchlorate and distilled as described above for deoxyprotoemetine.

(b) *Reduction by sodium borohydride.* A solution of the salt (XIV; $X^- = ClO_4^-$) (31 mg.) in methanol (5 ml.) was treated with sodium borohydride (13 mg.), acidified, and made strongly alkaline with potassium hydroxide. The product was extracted into ether, recovered by evaporation, and converted into the perchlorate in ethanol. The crystals obtained (23 mg.) recrystallised from aqueous ethanol to give the salt (17 mg.) obtained by method (*a*) above, m. p. and mixed m. p. 198—199°.

trans-3,4-*Diethylcyclopentanone* (XVI).—The crude ketone obtained by Koelsch and Stratton's simplified procedure [11] was redistilled and part (20 g.) was converted into the semicarbazone as usual. Recrystallisation from ethanol gave the pure semicarbazone (24·5 g.), m. p. 205—207° (decomp.) [lit.,[11] 202·5—206° (decomp.); lit.,[15] 208·5—209·5° (corr.)]. This was heated on the steam-bath for 1·5 hr. with concentrated hydrochloric acid (242 ml.) and water (215 ml.), cooled, and extracted thrice with ether, each ether layer being washed once with 5% potassium carbonate solution and once with water. After the combined ethereal solution had been dried, it was evaporated and the residue distilled completely at 85—86°/13 mm., to give pure *trans*-3,4-diethylcyclopentanone (14·8 g.).

XUM

Lactone (XVII) *of* threo-β*γ*-*Diethyl*-δ-*hydroxyvaleric Acid*.—This was prepared from *trans*-diethylcyclopentanone (13·76 g.) as described above for the *erythro*-lactone (XI); the threo-*lactone* had b. p. 140°/20 mm. It was purified on a column of silica gel; after elution with benzene and benzene–chloroform (1 : 1), the lactone was obtained by elution with chloroform. Distillation in a short-path still at 170° (bath)/30 mm. gave the analytical sample (Found: C, 68·8; H, 10·6. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%).

trans-1-(3,4-*Dimethoxyphenethyl*)-3,4-*diethyl*-2-*oxopiperidine* (XIX).—Treatment of the above lactone (9·75 g.) as described for the *erythro*-isomer yielded ethyl *threo*-β*γ*-diethyl-δ-bromovalerate (XVIII), b. p. 135—137°/14 mm. (12·9 g.) (Found: Br, 30·5. Calc. for $C_{11}H_{21}O_2Br$: Br, 30·2%). Part of this (3·19 g.) was used for the reaction with 3,4-dimethoxyphenethylamine as described above for the *cis*-isomer (XIII). The distilled product (3·5 g.), b. p. 180° (bath)/1·5 × 10^{-4} mm., was further purified on a column of silica gel by elution with benzene, benzene–chloroform (1 : 1), and chloroform. The last solvent yielded the trans-*oxopiperidone* (XIX) which was redistilled for analysis (Found: C, 70·9; H, 9·1; N, 4·1. $C_{19}H_{29}O_3N$ requires C, 71·45; H, 9·15; N, 4·4%). This distillate crystallised from ether–light petroleum and had m. p. 57—58°. The crystal form was lost completely when the solid was dried in a vacuum-desiccator at room temperature; this suggests that solvent of crystallisation is essential.

trans-5,11b-*Dehydro*-2,3-*diethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Perchlorate* (XX).—This preparation followed that of the *cis*-isomer (XIV). The *trans*-oxopiperidine (XIX) (1·04 g.) yielded the trans-*quinolizinium perchlorate* (XX) as prisms or metastable needles (1·12 g.) which after recrystallisation from aqueous ethanol (charcoal) had m. p. 165—166° after slight previous sintering (Found: C, 56·9; H, 7·2; N, 3·6. $C_{19}H_{28}O_6NCl$ requires C, 56·8; H, 7·0; N, 3·5%), $\nu_{max.}$ (in $CHCl_3$) 1647 cm.$^{-1}$ (C=N$^+$).

trans-2,3-*Diethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizine* (VII).—(a) *Catalytic reduction*. The foregoing salt (202 mg.) was hydrogenated (uptake 1·01 mol.) as described for the *cis*-isomer (XIV; $X^- = ClO_4^-$), to give the trans-*quinolizine perchlorate* (as VII), m. p. 211—213° (from aqueous ethanol) (148 mg.) (Found: C, 56·8; H, 7·8; N, 3·8. $C_{19}H_{30}O_6NCl$ requires C, 56·6; H, 7·5; N, 3·5%), $\lambda_{max.}$ 233, 285, $\lambda_{min.}$ 220, 256 (log ε 3·8, 3·54; 3·76, 2·61 respectively) in EtOH.

For infrared comparison with deoxyprotoemetine, the base was recovered from the pure perchlorate and distilled as for the *cis*-isomer.

(b) *Reduction by sodium borohydride*. The *trans*-salt (XX) (31 mg.) was reduced as for the *cis*-isomer, to give a crystalline perchlorate (27 mg.), m. p. 207—208° raised to 210—212°, alone or on admixture with the product from (*a*) above, by one recrystallisation from aqueous ethanol.

Reduction of the trans-*Salt* (XX) *with Zinc and Acetic Acid*.—A solution of this salt (887 mg.) in 50% aqueous acetic acid (50 ml.) was stirred at 60° with zinc dust (4 g.) for 24 hr. More zinc (3 g.) and glacial acetic acid (10 ml.) were then added and the stirring was continued for a further 70 hr. The solution was separated by decantation and, after the unused zinc had been washed with aqueous ethanol, the combined solutions were evaporated to dryness. The residue was dissolved in an excess of dilute hydrochloric acid, and the solution was extracted with ether. The aqueous solution was made strongly alkaline with sodium hydroxide and extracted thrice with ether, and the combined ethereal solution was extracted with 0·4N-hydrochloric acid (2 × 20 ml.). Evaporation of these acidic extracts left a solid which was shown by ultraviolet absorption measurements to contain less than 25% of starting material. It was dissolved in methanol (20 ml.), sodium borohydride (0·2 g.) was added portionwise in 5 min., and the solution was warmed at 50° for 0·5 hr. Water (30 ml.) was then added, the methanol was removed under reduced pressure, and, after the addition of a large excess of sodium hydroxide, the mixture was extracted with ether. Evaporation of the ethereal solution left a gum (587 mg.) which was converted into its perchlorate in aqueous solution as usual. This partly crystalline salt recrystallised from ethanol, to give the *trans*-diethylquinolizidine (VII) perchlorate (288 mg.), m. p. 205—208°, raised to 208—211°, after previous sintering in each case, on admixture with the pure salt from the foregoing experiment, section (*a*).

The bases were recovered as usual from the above ethanolic mother-liquors and were treated in ethanol with picric acid (0·4 g.); crystals separated (216 mg.), having m. p. 197—199°. These were recrystallised from methanol to give the trans-2,3-*diethylquinolizidine* (XXI) *picrate* as rhombs, m. p. 199—200° (Found: C, 56·9; H, 5·9. $C_{25}H_{32}O_9N_4$ requires C, 56·4; H, 6·05%).

A solution of the picrate (176 mg.) in chloroform was passed over alumina, and the column was eluted with chloroform. Evaporation of the eluate left the free base (XXI) as a thin gum (98 mg.). Part was distilled at 120°/0·05 mm. for analysis (Found: OMe, 20·5. $C_{19}H_{29}O_2N$ requires 2OMe, 20·4%). A further portion (9·7 mg.) was heated on the steam-bath with acetic anhydride (1 ml.) for 1 hr., and the excess of anhydride was then evaporated. The residue was separated into a neutral (trace) and a basic fraction (8·2 mg.) by partition as usual between ether and acid.

Mercuric Acetate Oxidation of the Base (XXI).—A solution of the foregoing base (23 mg.) and mercuric acetate (70 mg.) in 15% aqueous acetic acid (2 ml.) was heated under reflux for 6 hr. The mixture was worked up as described above for deoxyprotoemetine, a crystalline perchlorate (24 mg.) being obtained. This recrystallised from aqueous ethanol (charcoal), to give the *trans*-salt (XX) (17 mg.), m. p. and mixed m. p. 165—167°. The infrared spectrum (in Nujol) of this product was identical with that of the authentic *trans*-salt (XX).

Reduction of the trans-*Salt* (XX) *with Sodium and Alcohol.*—A solution of the salt (0·2 g.) in hot ethanol (30 ml.) was added dropwise to anhydrous ethanol (25 ml.) in which sodium (2 g.) was dissolving. After 15 min., more sodium (1 g.) was added and the solution was heated under reflux while addition of the solution containing the salt (XX) was continuing; the addition was carried out in 45 min. and all the sodium had dissolved after 1·5 hr. Water was added to the cooled solution, which was freed from ethanol by evaporation and then extracted with ether. Evaporation of the extracts left a gum (135 mg.). This was converted into the perchlorate in ethanol, and the crystals were collected (95 mg.), m. p. 170—182°; by five recrystallisations from ethanol, these yielded the *trans*-quinolizidine (VII) perchlorate (18 mg.), m. p. 203—205° raised to 207—210° in admixture with the sample of this salt prepared under (*a*) above. The two samples had identical infrared spectra (in Nujol).

Attempts were made to isolate the picrate of the base (XXI) from the various mother-liquors obtained in the above fractional crystallisation. Only a solid (47 mg.), m. p. 167—173° (decomp.), was obtained; the m. p. was raised to 172—176° by recrystallisation from ethanol. Recovery of the base from part of this picrate by passing a solution of it in chloroform over alumina gave a clear gum. This gave an infrared spectrum which was different from that given by the base (XXI).

Grateful acknowledgment is made to Professor G. W. Kenner, Dr. G. D. Meakins and Dr. G. F. Smith for the determination of many infrared spectra and to the Department of Scientific and Industrial Research for a Maintenance Award (to S. G.).

THE UNIVERSITY, BRISTOL. [*Received, May 25th,* 1959.]

---

708. *Physical Properties and Chemical Constitution. Part XXVII.* Dipole Moments of Some Cyclic Ethers, Sulphides, Sulphoxides, and Sulphones.*

By C. W. N. CUMPER and A. I. VOGEL.

The orientation polarisations and dipole moments of four cyclic organic sulphides, and the related sulphoxides and sulphones, have been calculated from measurements of the dielectric constants, specific volumes, and refractive indices of their solutions in benzene. The dipole moments are discussed in terms of the moment of the sulphur–oxygen link and the geometrical structure of the molecules. The dipole moments of five cyclic ethers have also been measured, and the carbon–oxygen bond moment evaluated and compared with that of non-cyclic ethers.

THE electric dipole moments of several organic sulphides, sulphoxides, and sulphones are recorded in the literature but only in four cases have the moments of the sulphide and the corresponding sulphoxide and sulphone been measured. No cyclic sulphoxides or sulphones have been investigated.

* Part XXVI, 1957, 3640.

XUM

The dipole moments of several cyclic organic sulphides and the related sulphoxides and sulphones, determined in benzene solution, are now reported and are discussed in terms of the moment of the sulphur–oxygen bond and the geometrical structure of the molecules. The dipole moments of some cyclic ethers are also considered.

Experimental

The apparatus and techniques used were described in Part XXV.[1] Observations were made in benzene solution at 25·00° ± 0·01°. The sulphoxides are hygroscopic and were handled in a dry box. Solutions of the more volatile ethers were prepared by adding the ether to the benzene in Pyrex glass-stoppered bottles so as to reduce loss by evaporation.

Thiacyclopentane oxide and dioxide, 1,4-thioxan, propene oxide, tetrahydrofuran, tetrahydropyran, and 1,3-dioxolan were high-grade commercial products; trimethylene oxide was prepared by Mr. D. G. Redford, B.Sc., and the other substances by Dr. R. S. Parker of this laboratory, who also extensively purified each compound. The sulphides, which were then used for the preparation of the sulphoxides and sulphones, and the ethers were tested for purity by gas-chromatography and shown to give one peak each (a Griffin & George Ltd. Mark IIA apparatus was used with silicone grease on Celite as the stationary phase). Details of the preparations, together with other physical properties, will be published later.

Results

The dielectric constants (ε_{12}), specific volumes (v_{12}), and refractive indices to sodium light (n_{12}) of benzene solutions with weight fractions w_2 are recorded in Table 1. Over the concentration range studied, ε_{12} was a linear function of w_2, and the parameters of this relation, determined by a method of least squares, are also in Table 1. Likewise v_{12} and the specific refraction (r_{12}) of the solutions were linear functions of w_2.

The total polarisation of the solutes, when extrapolated to infinite dilution, ($_\infty P_2$) was evaluated (see Table 2). The distortion polarisation, to be subtracted from $_\infty P_2$ to give the orientation polarisation ($_OP$), was assumed equal to the molar refraction to sodium light (R_D) and obtained from the specific refraction of the solutions.[1] The values of R_D, $_OP$ and the electric dipole moment (μ) of the compounds [calculated from the usual formula, $\mu = 0{\cdot}01281\sqrt{(_OPT)}$] are also given in Table 2. A large atom polarisation could result in a significant error in the dipole moment of 1,4-thioxan.

Discussion

(a) *Sulphides, Sulphoxides, and Sulphones.*—In a previous paper[2] the dipole moment change ($\Delta\mu_{SO}$) in the direction of the S–O bond, when a sulphide is converted into the sulphoxide or sulphone, was discussed. It was assumed that the CSC angle in the sulphides was unchanged on oxidation and that the oxygen atom(s) were always inclined at the same angle (θ) to the CSC plane. If θ was assigned the reasonable value of 61·5°, $\Delta\mu_{SO}$ was found to be 3·0 D in aliphatic sulphoxides and sulphones. This value is also in agreement with the dipole moments of several sulphones measured by Lumbroso and Passerini.[3]

A somewhat larger value for $\Delta\mu_{SO}$ is found if the sulphur atom is attached to a benzene ring—probably caused by larger induced moments and a change in the conjugation between them (the S–O bond is thought not to enter into conjugation [4]).

The results for the present compounds may be interpreted in two ways depending on the assumptions made.

(*a*) By applying vector analysis, as in the non-cyclic compounds considered previously,[2]

[1] Cumper, Vogel, and Walker, *J.*, 1956, **3621**.
[2] Cumper and Walker, *Trans. Faraday Soc.*, 1956, **52**, 193.
[3] Lumbroso and Passerini, *Bull. Soc. chim. France*, 1955, 1179.
[4] Price and Morita, *J. Amer. Chem. Soc.*, 1953, **75**, 4747; Price and Gillis, *ibid.*, 1953, **75**, 4750; Baliah and Shanmuganathan, *Trans. Faraday Soc.*, 1959, **55**, 232.

Table 1.

w_2	v_{12}	ϵ_{12}	n_{12}
Thiacyclobutane (1)			
0·000826	1·14430	2·2765	1·49788
0·002084	1·14408	2·2822	1·49790
0·005499	1·14352	2·2982	1·49791
0·008783	1·14293	2·3133	1·49790
0·012150	1·14240	2·3290	1·49794
0·016094	1·14172	2·3472	1·49798
0·017023	1·14158	2·3518	1·49800
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}149w_2)$			
$\epsilon_{12} = 2{\cdot}2726_2\ (1 + 2{\cdot}04_1w_2)$			
$r_{12} = 0{\cdot}33538\ (1 - 0{\cdot}135_2w_2)$			
Thiacyclobutane dioxide (2)			
0·000618	1·14419	2·2852	1·49770
0·001536	1·14380	2·3039	1·49770
0·004339	1·14257	2·3621	1·49767
0·007241	1·14125	2·4223	1·49769
0·012549	1·13892	2·5308	1·49766
0·013079	1·13860	2·5437	1·49766
0·016303	1·13720	2·6083	1·49765
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}387w_2)$			
$\epsilon_{12} = 2{\cdot}2724_4\ (1 + 9{\cdot}07_4w_2)$			
$r_{12} = 0{\cdot}33551\ (1 - 0{\cdot}397_2w_2)$			
Thiacyclopentane (3)			
0·000974	1·14430	2·2769	1·49776
0·001932	1·14421	2·2810	1·49777
0·004211	1·14383	2·2916	1·49778
0·006054	1·14357	2·2997	1·49778
0·010840	1·14289	2·3206	1·49780
0·015707	1·14218	2·3423	1·49784
0·017342	1·14193	2·3501	1·49785
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}126w_2)$			
$\epsilon_{12} = 2{\cdot}2726_4\ (1 + 1{\cdot}95_6w_2)$			
$r_{12} = 0{\cdot}33532\ (1 - 0{\cdot}117_8w_2)$			
Thiacyclopentane oxide (4)			
0·001563	1·14393	2·3008	1·49787
0·001633	1·14392	2·3022	1·49787
0·003154	1·14335	2·3293	1·49795
0·004937	1·14271	2·3634	1·49803
0·010235	1·14083	2·4593	1·49826
0·010306	1·14078	2·4608	1·49829
0·017860	1·13822	2·5978	1·49854
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}307w_2)$			
$\epsilon_{12} = 2{\cdot}2723_4\ (1 + 8{\cdot}02_8w_2)$			
$r_{12} = 0{\cdot}33536\ (1 - 0{\cdot}235_0w_2)$			

w_2	v_{12}	ϵ_{12}	n_{12}
Thiacyclopentane dioxide (5)			
0·000769	1·14409	2·2883	1·49787
0·000869	1·14408	2·2910	1·49784
0·003805	1·14288	2·3522	1·49788
0·005347	1·14222	2·3845	1·49792
0·007686	1·14116	2·4338	1·49800
0·010625	1·13995	2·4948	1·49805
0·018329	1·13670	2·6561	1·49820
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}370w_2)$			
$\epsilon_{12} = 2{\cdot}2726_1\ (1 + 9{\cdot}20_7w_2)$			
$r_{12} = 0{\cdot}33539\ (1 - 0{\cdot}333_8w_2)$			
Thiacyclohexane (6)			
0·000833	1·14435	2·2752	1·49776
0·002873	1·14410	2·2814	1·49777
0·003608	1·14400	2·2842	1·49777
0·008129	1·14344	2·2979	1·49779
0·012479	1·14290	2·3115	1·49781
0·016671	1·14238	2·3245	1·49784
0·018117	1·14220	2·3297	1·49784
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}108w_2)$			
$\epsilon_{12} = 2{\cdot}2726_3\ (1 + 1{\cdot}36_4w_2)$			
$r_{12} = 0{\cdot}33532\ (1 - 0{\cdot}100_4w_2)$			
Thiacyclohexane oxide (7)			
0·000300	1·14436	2·2775	1·49787
0·000946	1·14418	2·2873	1·49790
0·002025	1·14376	2·3053	1·49789
0·003407	1·14344	2·3274	1·49799
0·007500	1·14211	2·3936	1·49811
0·010272	1·14123	2·4386	1·49823
0·018072	1·13878	2·5652	1·49854
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}273w_2)$			
$\epsilon_{12} = 2{\cdot}2723_5\ (1 + 7{\cdot}13_4w_2)$			
$r_{12} = 0{\cdot}33538\ (1 - 0{\cdot}200_8w_2)$			
Thiacyclohexane dioxide (8)			
0·000396	1·14430	2·2801	1·49773
0·001080	1·14404	2·2929	1·49774
0·002717	1·14342	2·3238	1·49778
0·004228	1·14285	2·3524	1·49780
0·005788	1·14216	2·3820	1·49787
0·009178	1·14092	2·4455	1·49791
0·011789	1·13985	2·4946	1·49799
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}338w_2)$			
$\epsilon_{12} = 2{\cdot}2726_7\ (1 + 8{\cdot}28_8w_2)$			
$r_{12} = 0{\cdot}33530\ (1 - 0{\cdot}298_4w_2)$			

w_2	v_{12}	ϵ_{12}	n_{12}
1,4-Thioxan (9)			
0·002442	1·14382	2·2731	1·49781
0·008950	1·14214	2·2744	1·49790
0·016443	1·14021	2·2757	1·49800
0·021181	1·13895	2·2767	1·49808
0·027888	1·13729	2·2780	1·49811
0·032492	1·13606	2·2789	1·49820
0·036327	1·13506	2·2797	1·49825
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}226w_2)$			
$\epsilon_{12} = 2{\cdot}2725_7\ (1 + 0{\cdot}086_1w_2)$			
$r_{12} = 0{\cdot}33534\ (1 - 0{\cdot}204_2w_2)$			
1,4-Thioxan oxide (10)			
0·001937	1·14357	2·2879	1·49783
0·002788	1·14321	2·2943	1·49791
0·007551	1·14127	2·3314	1·49808
0·009052	1·14051	2·3436	1·49816
0·012377	1·13910	2·3693	1·49826
0·016411	1·13742	2·4007	1·49841
0·018652	1·13645	2·4187	1·49851
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}376w_2)$			
$\epsilon_{12} = 2{\cdot}2725_8\ (1 + 3{\cdot}44_3w_2)$			
$r_{12} = 0{\cdot}33533\ (1 - 0{\cdot}309_6w_2)$			
1,4-Thioxan dioxide (11)			
0·001203	1·14390	2·2828	1·49784
0·002228	1·14339	2·2917	1·49784
0·004603	1·14231	2·3120	1·49786
0·004827	1·14222	2·3141	1·49786
0·005047	1·14209	2·3162	1·49786
0·009678	1·13998	2·3561	1·49790
0·014300	1·13788	2·3959	1·49794
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}404w_2)$			
$\epsilon_{12} = 2{\cdot}2725_9\ (1 + 3{\cdot}79_4w_2)$			
$r_{12} = 0{\cdot}33536\ (1 - 0{\cdot}386_0w_2)$			
Propylene oxide (12)			
0·000531	1·14450	2·2761	1·49772
0·001075	1·14452	2·2800	1·49768
0·004845	1·14475	2·3050	1·49718
0·009235	1·14506	2·3344	1·49657
0·014399	1·14541	2·3689	1·49590
0·015948	1·14552	2·3794	1·49574
0·017908	1·14566	2·3924	1·49543
$v_{12} = 1{\cdot}14445\ (1 + 0{\cdot}067w_2)$			
$\epsilon_{12} = 2{\cdot}2726_2\ (1 + 2{\cdot}94_2w_2)$			
$r_{12} = 0{\cdot}33535\ (1 - 0{\cdot}168_4w_2)$			

w_2	v_{12}	ϵ_{12}	n_{12}
Trimethylene oxide (13)			
0·000682	1·14444	2·2768	1·49780
0·001457	1·14442	2·2819	1·49768
0·003741	1·14432	2·2973	1·49748
0·006317	1·14425	2·3143	1·49718
0·010801	1·14411	2·3435	1·49679
0·013239	1·14403	2·3599	1·49653
0·017177	1·14393	2·3855	1·49612
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}027w_2)$			
$\epsilon_{12} = 2{\cdot}2725_1\ (1 + 2{\cdot}89_4w_2)$			
$r_{12} = 0{\cdot}33537\ (1 - 0{\cdot}196_4w_2)$			
Tetrahydrofuran (14)			
0·000518	1·14445	2·2748	1·49776
0·001522	1·14444	2·2791	1·49769
0·004838	1·14438	2·2932	1·49743
0·005913	1·14434	2·2981	1·49728
0·009679	1·14425	2·3143	1·49692
0·013708	1·14419	2·3315	1·49661
0·014608	1·14415	2·3355	1·49650
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}017w_2)$			
$\epsilon_{12} = 2{\cdot}2725_4\ (1 + 1{\cdot}89_4w_2)$			
$r_{12} = 0{\cdot}33536\ (1 - 0{\cdot}173_1w_2)$			
Tetrahydropyran (15)			
0·000917	1·14445	2·2750	1·49783
0·001699	1·14444	2·2773	1·49774
0·004527	1·14441	2·2852	1·49753
0·006418	1·14439	2·2905	1·49741
0·009354	1·14435	2·2987	1·49717
0·014397	1·14429	2·3128	1·49674
0·017689	1·14426	2·3218	1·49652
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}010w_2)$			
$\epsilon_{12} = 2{\cdot}2725_7\ (1 + 1{\cdot}22_6w_2)$			
$r_{12} = 0{\cdot}33539\ (1 - 0{\cdot}139_2w_2)$			
1,3-Dioxolan (16)			
0·000942	1·14426	2·2754	1·49774
0·002122	1·14402	2·2786	1·49765
0·004601	1·14351	2·2863	1·49749
0·007754	1·14285	2·2951	1·49720
0·013463	1·14169	2·3117	1·49678
0·017560	1·14083	2·3236	1·49648
0·018262	1·14072	2·3259	1·49646
$v_{12} = 1{\cdot}14445\ (1 - 0{\cdot}179w_2)$			
$\epsilon_{12} = 2{\cdot}2726_0\ (1 + 1{\cdot}28_1w_2)$			
$r_{12} = 0{\cdot}33536\ (1 - 0{\cdot}309_1w_2)$			

Table 2.

Compound		${}_\infty P_2$ (cm.³)	R_D (cm.³)	${}_0P$ (cm.³)	μ_D	Previous vals. for C_6H_6 soln.
C_3H_6S	(1)	86·21	21·51	64·70	1·78	
$C_3H_6SO_2$	(2)	433·9	21·47	412·4	4·49	
C_4H_8S	(3)	99·98	26·09	73·89	1·90	1·87 [a]
C_4H_8SO	(4)	381·8	26·70	355·1	4·17	
$C_4H_8SO_2$	(5)	498·7	26·85	471·8	4·81	
$C_5H_{10}S$	(6)	90·86	30·83	60·03	1·71	
$C_5H_{10}SO$	(7)	389·7	31·71	358·0	4·19	
$C_5H_{10}SO_2$	(8)	505·7	31·56	474·1	4·82	
OC_4H_8S	(9)	31·33	27·80	3·53	0·42	0·47 [b]
OC_4H_8SO	(10)	202·3	27·82	174·5	2·92	
$OC_4H_8SO_2$	(11)	248·8	28·01	220·8	3·29	
$CH_2C_2H_3O$	(12)	94·02	16·21	77·81	1·95	1·88 [c], 1·98 [d]
C_3H_6O	(13)	91·20	15·65	75·55	1·92	2·01 [c]
C_4H_8O	(14)	82·55	20·00	62·55	1·75	1·68 [a], 1·71 [e]
$C_5H_{10}O$	(15)	74·22	24·87	49·35	1·55	1·87 [c]
$C_2H_6O_2$	(16)	61·28	17·15	44·13	1·47	
RR′S *					1·59	
RR′SO_2 *					4·46	

* Average values [a] for R, R′ = Et, Pr^n, Bu^n, n-C_5H_{11}.

[a] Robles, *Rec. Trav. chim.*, 1939, **58**, 111. [b] Henriques, *ibid.*, 1934, **53**, 1139; Boeseken, Tellegen, and Henriques, *ibid.*, 1935, **54**, 733. [c] Allen and Hibbert, *J. Amer. Chem. Soc.*, 1934, **56**, 1398. [d] Rogers, *ibid.*, 1947, **69**, 2544. [e] Smyth and Walls, *ibid.*, 1932, **54**, 3230.

XUM

the results in Table 3 are obtained. Column 2 gives the values evaluated for $\Delta\mu_{SO}$ if the angle θ is assumed to be 61·5°; column 3 gives the angle θ required to account for the experimental dipole moments if $\Delta\mu_{SO}$ is taken as 3·00 D. In this analysis an additional assumption is made, that the resultant moment of the sulphide acts in the CSC plane.

TABLE 3.

Compound		$\Delta\mu_{SO}$ (θ = 61·5°)	θ ($\Delta\mu_{SO}$ = 3·00 D)	Compound		$\Delta\mu_{SO}$ (θ = 61·5°)	θ ($\Delta\mu_{SO}$ = 3·00 D)
$C_3H_6SO_2$	(2)	2·84 D	63·1°	$C_5H_{10}SO_2$	(8)	3·25	58·8°
C_4H_8SO	(4)	2·91	65·3	OC_4H_8SO	(10)	2·70	104·1
$C_4H_8SO_2$	(5)	3·04	61·0	$OC_4H_8SO_2$	(11)	3·01	61·4
$C_5H_{10}SO$	(7)	3·09	57·1	$RR'SO_2$		3·01	61·4

(*b*) Thiacyclobutane almost certainly has a planar ring [5] but it has been reported that this is not the case for cyclopentane [6] and it would be less likely for thiacyclopentane.[7] Thiacyclohexane [8] and 1,4-thioxan have distorted chair conformations. Consequently, since the C–H bond is polar [9] the resultant moments of thiacyclopentane, thiacyclohexane, and 1,4-thioxan cannot lie in the CSC plane.

The dipole moments of the cyclic sulphides, sulphoxides, and sulphones may be expressed by the following equations, in which X is the resultant (opposing) dipole moment of the C–H bonds (together with the C–O bonds in 1,4-thioxan) and the induced moments in the C–C bonds, and ϕ the angle between the direction of X and the resultant moment of the two C–S bonds (μ_{CS}).

Sulphide

$$\mu^2 = [2\mu_{CS}\cos\frac{\angle CSC}{2} + X\cos\phi]^2 + [X\sin\phi]^2$$

Sulphoxide

$$\mu^2 = [2\mu_{CS}\cos\frac{\angle CSC}{2} + X\cos\phi + \Delta\mu_{SO}\cos\theta]^2 + [X\sin\phi \pm \Delta\mu_{SO}\sin\theta]^2$$

Sulphone

$$\mu^2 = [2\mu_{CS}\cos\frac{\angle CSC}{2} + X\cos\phi + 2\Delta\mu_{SO}\cos\theta]^2 + [X\sin\phi]^2$$

The angle θ can be evaluated from the above equations if one assumes that the angle CSC is constant and that $\Delta\mu_{SO}$ is 3·00 D in both sulphoxides and sulphones; the results are presented in Table 4. The CSO angle is remarkably constant in many sulphoxides and sulphones [10] at about 107°, and if this value is assumed for these cyclic molecules the CSC angle may be calculated from the relation:

$$-\cos\angle CSO = \cos\tfrac{1}{2}\angle OSO\cos\tfrac{1}{2}\angle CSC$$

In each case the results seem plausible and the relative values consistent. Since $\Delta\mu_{SO}$ and θ are not independent of one another, the angles θ for the cyclic compounds will depend on the value of θ assumed for the alkyl sulphoxides and sulphones. It is also possible that $\Delta\mu_{SO}$ may differ slightly between a sulphoxide and the corresponding sulphone; but the experimental data are at present insufficient to decide this point. Further, if the $\overset{+}{C}\!\!\rightarrow\!\!S$

[5] Scott, Finke, Hubbard, McCullough, Katz, Gross, Messerly, Pennington, and Waddington, *J. Amer. Chem. Soc.*, 1953, **75**, 2795.
[6] Kilpatrick, Pitzer, and Spitzer, *ibid.*, 1947, **69**, 2483; Miller and Inskeep, *J. Chem. Phys.*, 1950, **18**, 1510; Le Fèvre and Le Fèvre, *Chem. and Ind.*, 1956, 54.
[7] Hubbard, Finke, Scott, McCullough, Katz, Gross, Messerly, Pennington, and Waddington, *J. Amer. Chem. Soc.*, 1952, **74**, 6025.
[8] McCullough, Finke, Hubbard, Good, Pennington, Messerly, and Waddington, *ibid.*, 1954, **76**, 2661.
[9] Smith, "Electric Dipole Moments," Butterworths, London, 1955, p. 125.
[10] Abrahams, *Quart. Rev.*, 1956, **10**, 407.

bond moment μ_{CS} is known, X and ϕ can also be evaluated, though they have little significance. The values quoted in Table 4 are evaluated on the assumption that $\mu_{CS} = 1{\cdot}60$ D.†

In thiacyclobutane the CSC angle would be between the bonding orbitals of the sulphur atom rather than the actual bond angle. The above analysis shows that the S–O and X moments are *trans* to one another in the thiacyclopentane and 1,4-thioxan oxides, but *cis* in thiacyclohexane oxide. The oxide oxygen atom is probably in the equatorial position in each case.

TABLE 4.

Compounds	θ	∠CSC	ϕ	X (D)
C_3H_6S (1), $C_3H_6SO_2$ (2)	63·1°	99·4°	0·0°	−0·29
C_4H_8S (3), C_4H_8SO (4), $C_4H_8SO_2$ (5)	61·0	105·8	72·5	−0·15
$C_5H_{10}S$ (6), $C_5H_{10}SO$ (7), $C_5H_{10}SO_2$ (8)	58·9	111·0	27·6	−0·11
OC_4H_8S (9), OC_4H_8SO (10), $OC_4H_8SO_2$ (11)	60·3	107·8	10·4	−1·61
RR′S, RR′SO_2	61·4	104·5	0·0	−0·37

(b) *Ethers.*—The dipole moments of some cyclic ethers were measured for comparison with the cyclic sulphides. Since the C–O bond is shorter than a C–S bond, ring systems containing oxygen would be expected to be less distorted than the corresponding sulphides.

The apparent C–O bond moments, without allowance for induced moments, calculated for various COC bond angles are given in Table 5 ($\mu_{C\rightarrow H} = 0{\cdot}30$ D).

The boiling point of ethylene oxide is somewhat low for this compound to be studied adequately in solution (its dipole moment has been reported [11] as 1·88 and 1·85 D), but should be slightly less than that of propylene oxide because of the moment induced in the methyl group. The dipole moments of ethylene oxide and trimethylene oxide in the vapour phase are 1·91 and 1·94 D respectively.[12] The C–O bonds are bent considerably in these molecules, and their calculated bond moments have no general significance. The COC angle in trimethyl oxide [10] has been determined as 94·5° ± 3°, though the bonds are probably slightly bent; in tetrahydrofuran the COC angle would be 102° if the CCC angles had their normal tetrahedral value: and 106° in 1,3-dioxolan.

The dipole moment of 1,3-dioxolan does not seem consistent with the results for the other cyclic ethers, yet it was completely reproducible. The dipole moments of several alkyl substituted 1,3-dioxolans have been reported to lie [13] between about 1·1 and 1·3 D. The substituents however were mainly in position 2, where the induced moments would lower the dipole moment. It is rather unlikely that the molecule is non-planar, but since the C–O bonds are about 0·11 Å shorter than C–C bonds the OCO angle must be

TABLE 5.

Compound		μ (D) at COC angles 90°	94·5°	102°	106°	109·5°
C_2H_4O	(13)	1·61	1·67			
C_4H_8O	(14)		1·57	1·69	1·77	1·84
$C_5H_{10}O$ *	(15)		1·40	1·51	1·57	1·64
$C_2H_4O_2$	(16)			2·31	2·31	2·32
$(CH_3)_2O$			1·25	1·33	1·37	1·42

* The results for this molecule depend only slightly on the extent to which its structure departs from the chair conformation of cyclohexane, with all the bond angles 109·5°.

greater than 109·5°; a OCO angle of 120° would give a C–O bond moment of about 1·72 D in much better agreement with the other values of Table 5.

† If ∠CSC is 109·5°, then $\mu_{CS} = 1{\cdot}52$ D if the moment of Me_2S is employed,[3] but 1·68 D from the dipole moment of $Pr^n{}_2S$ where a contribution from induced moments in the alkyl chains is included. A bond angle 5° smaller would imply C–S bond moments of 1·45 and 1·60 D respectively ($\mu_{C\rightarrow H} = 0{\cdot}30$ D).

[11] Stuart, *Z. Physik*, 1928, **51**, 490; Hibbert and Allen, *J. Amer. Chem. Soc.*, 1932, **54**, 4115; Angyal, Barclay, and Le Fèvre, *J.*, 1950, 3370.

[12] Gent, *J.*, 1957, 58.

[13] Otto, *J. Amer. Chem. Soc.*, 1937, **59**, 1590; Bergmann, Fischer, Zimkin, and Pinchas, *Rec. Trav. chim.*, 1952, **71**, 213.

Methyl ether with a dipole moment of 1·29 D in the vapour phase, and 1·25 D in benzene solution,[14] has a low apparent C–O bond moment because of greatly reduced contributions from induced moments, and the same is true for diethyl and di-n-propyl ether.[14] The COC angle[15] in dimethyl ether is about 111° and the C–O bond moment in solution is consequently about 1·41 D; it appears that the apparent C–O moment in cyclic ethers, where the contributions from induced moments are clearly greater, is about 1·66 D.

The authors wish to thank Imperial Chemical Industries Limited for a grant.

CHEMISTRY DEPARTMENT, WOOLWICH POLYTECHNIC,
LONDON, S.E.18. [*Received, March 13th*, 1959.]

[14] Barclay and Le Fèvre, *J.*, 1952, 1643.
[15] Kimura and Kubo, *J. Chem. Phys.*, 1959, **30**, 151.

---

709. *Methylperylenes. Part I. Synthesis of* 1-, 2-, *and* 3-*Methylperylene.*

By A. D. CAMPBELL, R. A. ELDER, and G. W. EMERSON.

The three monomethylperylenes have been synthesised and their ultraviolet spectra determined. 1-Methylperylene was prepared by the cyclodehydrogenation of a methyl-1,1′-binaphthyl; 2-methylperylene from 2-methylanthracene by a variation of a Postovskii and Bednyagina [1] perylene synthesis; and 3-methylperylene by a modification of Buu-Hoï's method [2] from 3-formylperylene.

DURING a recent investigation [3] on the structure of a fungus pigment, degradative work yielded small amounts of a hydrocarbon, the ultraviolet absorption spectrum of which agreed closely with that reported for perylene. Since insufficient material was available for analysis the possibility of the hydrocarbon's being an alkylperylene could not be overlooked, particularly since only one perylene homologue was then known and its spectrum had not been recorded. Plausible biogenetic schemes would allow the pigment to be related to 2,8- or 2,11-dimethylperylene, and initially the synthesis of the former was undertaken. It seemed of interest to examine further the effect of alkyl-substitution on the physical properties of perylene, and a number of methyl- and dimethyl-perylenes have been synthesised for this purpose.

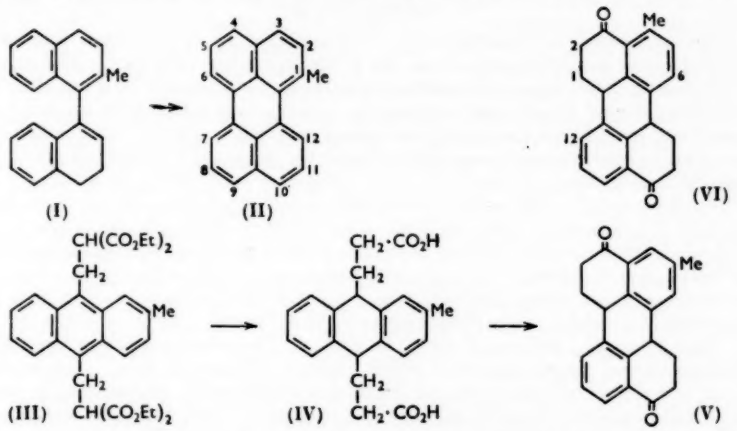
1-*Methylperylene.*—Some difficulty was experienced in synthesising this compound but success was finally attained by using a methylbinaphthyl as intermediate. Condensation of the lithium derivative from 1-bromo-2-methylnaphthalene with α-tetralone gave a poor yield of 3,4-dihydro-2′-methyl-1,1′-binaphthyl (I) as a glass, and dehydrogenation of this with palladium on charcoal led to 2-methyl-1,1′-binaphthyl and 1-methylperylene (II). The latter hydrocarbon gave two derivatives with picric acid, a black monopicrate under controlled conditions, and a brick-red dipicrate in the presence of excess of picric acid.

Other methods were unsuccessful. Chloromethylation of 1-methylanthracene was unsatisfactory, preventing the use of the Postovskii and Bednyagina perylene synthesis as adapted to the preparation of 2-methylperylene below. In another investigation no perylene derivative was isolated on dehydrogenation of the product obtained from crotonaldehyde and tetrahydrobenzanthrone in hydrogen fluoride, although Calcott *et al.*[4] obtained perylene by this method, condensing acraldehyde with tetrahydrobenzanthrone.

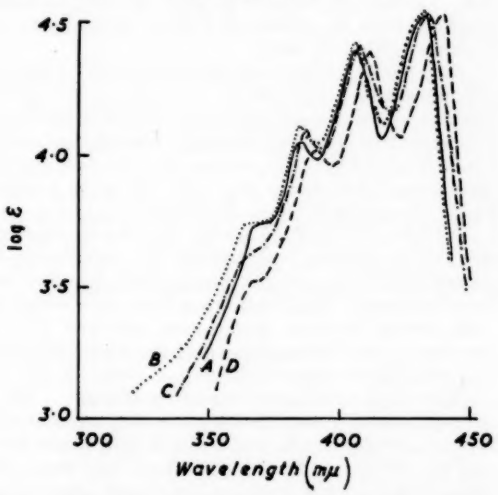
2- *and* 3-*Methylperylene.*—2-Methylperylene was obtained by making use of a series of

[1] Postovskii and Bednyagina, *J. Gen. Chem.* (*U.S.S.R.*), 1937, **7**, 2919.
[2] Buu-Hoï, *Rec. Trav. chim.*, 1956, **75**, 1221.
[3] Anderson and Murray, *Chem. and Ind.*, 1956, 376.
[4] Calcott, Tinker, and Weinmayer, *J. Amer. Chem. Soc.*, 1939, **61**, 949.

reactions similar to the Postovskii and Bednyagina [1] synthesis of perylene. The 9,10-bischloromethyl derivative of 2-methylanthracene with diethyl malonate gave a tetracarboxylic ester (III) which on hydrolysis and decarboxylation gave 9,10-di-(2-carboxyethyl)-2-methylanthracene. This acid was not cyclised directly but was reduced to the



dihydroanthracene derivative (IV), which was smoothly cyclised by anhydrous hydrogen fluoride to a mixture of the two possible dioxoperylenes. The minor constituent of this mixture, on reduction and dehydrogenation, gave 3-methylperylene identical with that



Ultraviolet absorption spectra of (A) perylene and (B) 1-, (C) 2-, and (D) 3-methylperylene in 95% ethanol.

prepared from perylene by Buu-Hoï.[2] It must therefore be 1,2,3,6b,7,8,9,12b-octahydro-4-methyl-3,9-dioxoperylene (VI). The other isomer (V) afforded 2-methylperylene when similarly reduced and dehydrogenated. Although it would also be possible to obtain a derivative of 1,2-benzopyrene in this cyclisation there was no evidence for the presence of such a compound.

Buu-Hoï [2] describes a synthesis of 3-methylperylene *via* 3-formylperylene but gives no ultraviolet spectrum. We have repeated the formylation of perylene and have simplified the reduction of this substance to 3-methylperylene.

Spectra.—The principal peaks in the ultraviolet absorption spectra of perylene and its three monomethyl derivatives are tabulated on p. 3529 and the spectra in the region 340—450 mμ are shown in the Figure.

Experimental

3,4-*Dihydro*-2′-*methyl*-1,1′-*binaphthyl* (I).—Lithium (2·8 g.) in thin slices was added to a solution of 1-bromo-2-methylnaphthalene (44 g.) in dry ether (300 c.c.). The mixture was stirred at reflux for 3 hr., most of the lithium dissolving. α-Tetralone (29 g.) in ether (100 c.c.) was then added during 45 min. and the resulting solution was refluxed for a further 2 hr. It was poured into ice-cold sulphuric acid, and the ether layer was dried and distilled, to give a mixture of unchanged starting materials, followed by the *dihydro-binaphthyl* (I) (5 g.), b. p. 250—260°/20 mm. (Found: C, 92·9; H, 6·6. $C_{21}H_{18}$ requires C, 93·3; H, 6·7%).

1-*Methylperylene* (II).—The above dihydrobinaphthyl (3 g.) was refluxed (bath 340—350°) for 3 hr. with 5% palladium–charcoal (1 g.) in a stream of carbon dioxide. The cooled mass was taken up in the minimum quantity of hexane containing a trace of benzene and chromatographed on an alumina column. Elution with hexane gave a colourless band which showed a blue fluorescence under ultraviolet radiation. Concentration of this fraction gave **2-*methyl*-1,1′-*binaphthyl*** (2 g.) which, after recrystallisation from hexane, had m. p. 120—122° (Found: C, 94·0; H, 5·8. $C_{21}H_{16}$ requires C, 94·0; H, 6·0%). The remaining yellow band was eluted with benzene–hexane which deposited yellow crystals on concentration. This material was filtered off and converted into a picrate which was subsequently decomposed in benzene on alumina. Yellow plates of **1-*methylperylene*** (30 mg.), m. p. 258—260° with sintering at 220°, were obtained by crystallisation from benzene–hexane (Found: C, 94·7; H, 5·0. $C_{21}H_{14}$ requires C, 94·7; H, 5·3%). It gave a ***monopicrate*** as black needles (from benzene–hexane), m. p. 191—192° (Found: C, 65·3; H, 3·0; N, 8·3. $C_{27}H_{17}O_7N_3$ requires C, 65·45; H, 3·5; N, 8·5%), a ***dipicrate*** as brick-red needles (from benzene), m. p. 186—187° (Found: C, 54·0; H, 2·7. $C_{33}H_{20}O_{14}N_6$ requires C, 54·6; H, 2·8%), and the ***derivative*** with trinitrobenzene as dark purple needles, m. p. 242—243° (from benzene–hexane) (Found: C, 67·3; H, 3·5. $C_{27}H_{17}O_6N_3$ requires C, 67·6; H, 3·5%).

9,10-*Bischloromethyl*-2-*methylanthracene*.—2-Methylanthracene (16·5 g.) and paraformaldehyde (15 g.) were added to a mixture of dioxan (150 c.c.) and concentrated hydrochloric acid (25 c.c.) which had been previously saturated with dry hydrogen chloride. The whole was boiled for 2 hr. while dry hydrogen chloride was added, and for a further 3 hr., then cooled and set aside for 12 hr. The crystals (17 g.) which separated recrystallised from dioxan, giving the ***bischloromethyl derivative*** as yellow needles, m. p. 229—231° (decomp.) (Found: C, 70·7; H, 5·0. $C_{17}H_{14}Cl_2$ requires C, 70·6; H, 4·8%).

9,10-*Bis*-(2,2-*diethoxycarbonylethyl*)-2-*methylanthracene* (III).—Diethyl malonate (18·2 g.) was added dropwise with stirring to a solution made by adding sodium (2·6 g.) to pure dry ethanol (200 c.c.), and the mixture was stirred at the b. p. for a further 30 min. The above bischloromethyl compound (14 g.) was then added all at once, and the mixture was refluxed with stirring for 2 hr. and poured into cold water slightly acidified with acetic acid. The precipitate was filtered off to give the ***tetra-ethyl ester*** (III) (21 g.) as pale yellow needles, m. p. 140—141° (from ethanol) (Found: C, 69·8; H, 6·7. $C_{31}H_{36}O_8$ requires C, 69·4; H, 6·8%).

9,10-*Di*-(2-*carboxyethyl*)-2-*methylanthracene*.—The above ester (23 g.) was refluxed for 4 hr. with potassium hydroxide (50 g.) in 50% aqueous ethanol (200 c.c.). The cooled solution was filtered and the filtrate was acidified with dilute hydrochloric acid. The resulting precipitate was filtered off, air-dried (yield, 12 g.), and then refluxed in diphenyl ether (50 c.c.) for 1 hr. Ether (100 c.c.) was added to the cooled solution, and the acid which crystallised (3 g.) was filtered off. Further acid (4 g.) was obtained by extracting the filtrate with aqueous sodium hydroxide. Recrystallisation of the combined acids from benzene containing a trace of ethanol gave the ***dipropionic acid*** (5·8 g.) as pale yellow needles, m. p. 215—216° (Found: C, 75·0; H, 6·0. $C_{21}H_{20}O_4$ requires C, 75·0; H, 6·0%).

9,10-*Di*-(2-*carboxyethyl*)-9,10-*dihydro*-2-*methylanthracene* (IV).—Sodium (20 g.) was added in small portions during 12 hr. to the above dipropionic acid (5·8 g.) in boiling pentyl alcohol (150 c.c.). The mixture was cautiously poured into water and the pentyl alcohol was removed by steam-distillation. The aqueous solution was filtered, then acidified with dilute hydrochloric acid, and the resulting white solid was filtered off. Recrystallisation from ethanol gave

the *dihydro-compound* (4·0 g.) as white plates, m. p. 228° (Found: C, 74·2; H, 6·1. $C_{21}H_{22}O_4$ requires C, 74·5; H, 6·55%).

Cyclisation of 9,10-*Di*-(2-*carboxyethyl*)-9,10-*dihydro*-2-*methylanthracene*.—The above dihydroanthracene derivative (0·6 g.) was treated with anhydrous hydrogen fluoride (30 c.c.) at room temperature. After 24 hr. the resulting solution was poured on ice, and the solid material was filtered off, taken up in ethyl acetate, and washed with aqueous sodium carbonate. Neutral cyclised material (0·2 g.) which separated on concentration of the ethyl acetate solution was further recrystallised from ethyl acetate, to give 1,2,3,6*b*,7,8,9,12*b*-*octahydro*-5-*methyl*-3,9-*dioxoperylene* (V) (0·18 g.) as pale green needles, m. p. 215—217° (decomp.) (Found: C, 83·2; H, 6·0. $C_{21}H_{18}O_2$ requires C, 83·4; H, 6·0%). The mother-liquors from the above crystallisations, on concentration, gave red crystals which on further recrystallisation from ethyl acetate (charcoal) gave 1,2,3,6*b*,7,8,9,12*b*-*octahydro*-4-*methyl*-3,9-*dioxoperylene* (VI) (0·05 g.) as brick-red crystals, m. p. 193—194° (Found: C, 83·6; H, 5·8. $C_{21}H_{18}O_4$ requires C, 83·4; H, 6·0%). The latter compound gave 3-methylperylene, m. p. 214—215°, on reduction with lithium aluminium hydride followed by dehydration and dehydrogenation in refluxing 2-methylnaphthalene in the presence of palladium–charcoal.

2-*Methylperylene*.—1,2,3,6b,7,8,9,12b-Octahydro-5-methyl-3,9-dioxoperylene (V) (0·15 g.) was extracted with refluxing ether into excess of lithium aluminium hydride (0·3 g.) in dry ether (200 c.c.) during 8 hr. Excess of reagent was decomposed by ethyl acetate, the resulting solution was poured into ice and dilute sulphuric acid, the ether layer was separated, and the aqueous solution extracted with ether. The residue obtained on evaporation of the combined ether extracts was refluxed in 2-methylnaphthalene (20 g.) in the presence of 5% palladium–charcoal (0·1 g.) for 8 hr. Hexane (100 c.c.) was added to the cooled mixture, and the resulting solution was applied to a column of alumina. 2-Methylnaphthalene was eluted with hexane, and the residual yellow band with benzene–hexane mixtures, to give 2-*methylperylene* (0·07 g.) as yellow prisms, m. p. 168° (from ethanol) (Found: C, 94·65; H, 5·4. $C_{21}H_{14}$ requires C, 94·7; H, 5·3%). It gave a *picrate* as dark brown needles, m. p. 199—200° (decomp.) (from benzene–hexane) (Found: C, 65·45; H, 3·2; N, 8·5. $C_{27}H_{17}O_7N_3$ requires C, 65·5; H, 3·5; N, 8·5%), and a *derivative* with trinitrobenzene as red needles, m. p. 227—228° (decomp. at 220°) (from benzene–ethanol) (Found: C, 67·8; H, 3·1. $C_{27}H_{17}O_6N_3$ requires C, 67·6; H, 3·5%).

3-*Methylperylene*.—3-Formylperylene (0·25 g.) and 85% hydrazine hydrate (0·5 c.c.) were heated in a sealed tube for 5 hr. at 300°. The resulting red solid in benzene was purified on an alumina column, and the eluate was concentrated, to give the hydrocarbon (0·18 g.) as golden plates, m. p. 214° (Buu-Hoï gave m. p. 217°) (Found: C, 94·6; H, 5·2. Calc. for $C_{21}H_{14}$: C, 94·7; H, 5·3%). It gave a picrate as black needles, m. p. 220° with previous softening (Buu-Hoï gives m. p. 226° with decomp. below 212°) (Found: C, 65·5; H, 3·2. Calc. for $C_{27}H_{17}O_7N_3$: C, 65·45; H, 3·5%), and a trinitrobenzene *derivative* as long dark purple needles, m. p. 242° (from benzene–ethanol) (Found: C, 67·8; H, 3·3. $C_{27}H_{17}O_6N_3$ requires C, 67·6; H, 3·5%).

Absorption Spectra.—Ultraviolet absorption spectra were obtained on a Beckman Model DK2 Spectrophotometer by courtesy of the Nutrition Research Department, Otago Medical School, as tabulated.

Absorption spectra (mμ *and* log ε) in 95% *ethanol*.

Perylene	208	245	252	266 (infl.)	364 (infl.)	385	406·5	434
	4·73	4·52	4·66	3·93	3·60	4·05	4·40	4·54
1-Methylperylene	208	245	252	268 (infl.)	367 (infl.)	384	406	433·5
	4·72	4·52	4·65	3·88	3·70	4·10	4·40	4·52
2-Methylperylene	208	246·5	253	266 (infl.)	370 (infl.)	387	408	435
	4·76	4·51	4·65	3·97	3·90	4·08	4·41	4·53
3-Methylperylene ...	—	246·5	254	268 (infl.)	370 (infl.)	391	412·5	440
	—	4·46	4·61	3·85	3·53	4·02	4·39	4·53

This work has been assisted by grants from the Research Fund of the University of New Zealand and from the Mellor Research Fund. Microanalyses were carried out by the Microanalytical Laboratory of this Department.

CHEMISTRY DEPARTMENT, UNIVERSITY OF OTAGO,
NEW ZEALAND.

[*Received, April 13th*, 1959.]

XUM

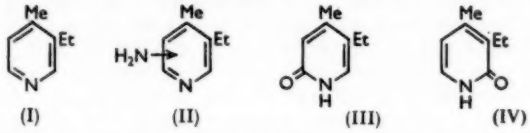
710. *Chemical Constitution and Amœbicidal Action. Part IV.* Synthesis of Emetine and Stereoisomers of Emetine.*

By M. Barash, J. M. Osbond, and J. C. Wickens.

Stereoisomers of emetine (XXII) have been synthesised by three routes: (1) Catalytic reduction of the four dehydroemetines (XXI) has given 4 stereoisomers of emetine (XXII) (Aa_1, Ab_2, Bc_1, and Bd_1). Paper chromatography showed only one of these isomers (Aa_1) to be inseparable from emetine. The physicochemical properties were in close agreement with those of emetine, and (±)-Aa_1 had slightly more than half the amœbicidal activity of (+)-emetine dihydrochloride. Resolution of the base of (±)-Aa_1 gave optically active salts indistinguishable from natural emetine salts. (2) Catalytic reduction of tetradehydroemetinium chloride hydrochloride (XXIII; A) led to the predominant formation of (±)-isoemetine (Ab_2) with a small amount of (±)-emetine (Aa_1). (3) Catalytic reduction of the esters (XXV; A and B) with subsequent transformations led to the formation of the above four emetine isomers.

The correct structure (XXII) for emetine, suggested by Robinson [1] on biogenetic grounds, was confirmed independently by Openshaw [2] and Pailer [3] and their co-workers, and (±)-rubremetinium bromide has been synthesised by three groups of workers.[4,5,6] In addition a total synthesis of emetine has been described by Preobrazhenskii and Evstigneeva and their co-workers,[7] and a partial synthesis by Battersby, Davidson, and Harper.[8] A summary [9] of our synthetic work was followed by a stereospecific synthesis of emetine by Battersby and Turner,[10] which caused us to re-examine some of our conclusions and to make a correction.[11]

As emetine (XXII) has four asymmetric centres (positions 2, 3, 11b, and 1'), 8 racemic and 16 optical isomers are possible. To apply the synthesis of de-ethylemetine, described in Part III,* to emetine, it was necessary to prepare the pyridone (III).

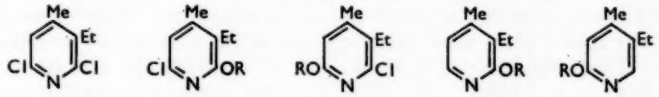


β-Collidine (I) with sodamide in dimethylaniline gave a mixture of the 2- and 6-aminopyridine (II) which was converted into the pyridones (III) and (IV) and separated by crystallisation, but the yield was low and the unwanted isomer (IV) predominated. An alternative route employed 2,6-dichloro-5-ethyl-4-methylpyridine [12] (V) which with one

* Part III, *J.*, 1959, 2157.

[1] Robinson, *Nature*, 1948, **162**, 524.
[2] Battersby and Openshaw, *J.*, 1949, 559, 567, 3207.
[3] Pailer, *Monatsh.*, 1948, **78**, 331; Spath and Pailer, *ibid.*, p. 348; Pailer, *ibid.*, 1948, **79**, 127; Pailer and Porschinski, *ibid.*, 1949, **80**, 94.
[4] Battersby, Openshaw, and Wood, *J.*, 1953, 2463.
[5] Ban, *Pharm. Bull.* (*Japan*), 1955, **3**, 47.
[6] Pailer and Beier, *Monatsh.*, 1957, **88**, 830.
[7] Preobrazhenskii, Evstigneeva, Levchenko, and Fedyushkina, *Doklady Akad. Nauk S.S.S.R.*, 1951, **81**, 421; Evstigneeva, Livshits, Bainova, Zakharkin, and Preobrazhenskii, *Zhur. obschei Khim.*, 1952, **22**, 1467; Evstigneeva, *ibid.*, 1958, **28**, 2458; Evstigneeva, Glushkov, and Preobrazhenskii, *ibid.*, p. 2463.
[8] Battersby, Davidson, and Harper, *Chem. and Ind.*, 1957, 983.
[9] Barash and Osbond, XVIth Internat. Congr. Pure Appl. Chem., Paris, 1957; Barash and Osbond, *Chem. and Ind.*, 1958, 490.
[10] Battersby and Turner, *Chem. and Ind.*, 1958, 1324; cf. Burgstahler and Bithos, *J. Amer. Chem. Soc.*, 1959, **81**, 503.
[11] Osbond, *Chem. and Ind.*, 1959, 257.
[12] Ruzicka and Fornasir, *Helv. Chim. Acta*, 1919, **2**, 338.

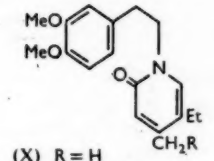
equivalent of sodium isopropoxide, sodium benzyloxide, or potassium diphenylmethoxide gave a mixture of the isomers (VI) and (VII) (R = Pr^i, CH_2Ph, or $CHPh_2$). It was hoped



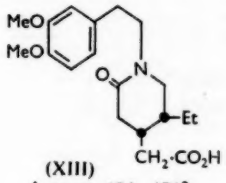
(V) (VI) (VII) (VIII) (IX)

that the condensation with a bulky group (*e.g.*, diphenylmethyl) would occur chiefly at the less hindered 2-position. The mixture (VI + VII; R = Pr^i) was dechlorinated by hydrogenolysis to give the ethers (VIII + IX; R = Pr^i) which on acid hydrolysis gave the pyridones (III; 47%) and (IV; 9%). Alternatively, the mixture (VI + VII; R = Pr^i) was hydrolysed and then dechlorinated. The mixture of benzyl ethers (VI + VII) was hydrogenated to give predominantly the pyridone (III). The condensation with potassium diphenylmethoxide was the most favourable as it gave chiefly the ether (VII; R = $CHPh_2$). Hydrogenolysis gave the pure pyridone (III) in one step.

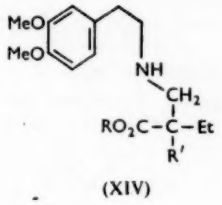
The structures of the pyridones (III) and (IV) were assigned on the following considerations. By analogy [13] it was expected that, in the amidation of β-collidine (I), isomer (IV) would predominate, whereas in the condensation of the dichloro-compound (V) with potassium diphenylmethoxide the isomer (III) was expected. The pyridone (III) had $\lambda_{max.}$ 298 mμ, and the isomer (IV) 293 mμ; 5- and 3-methyl-2-pyridones [13] showed a parallel difference, namely 303 and 295 mμ respectively (cf. also ref. 14). Compound (III) was converted into the two acetic acid derivatives (XIII; A and B) (see below) which were identical with those obtained by a different route [5] and were converted eventually into (±)-rubremetinium bromide (XXIV).



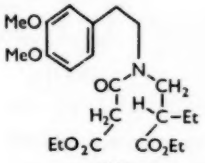
(X) R = H
(XI) R = CO·CO_2Et
(XII) R = CO_2H



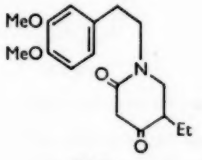
(XIII)
A, m.p. 154–156°
B, m.p. 152–153°



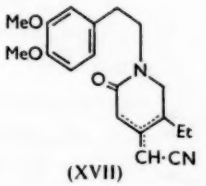
(XIV)



(XV)



(XVI)

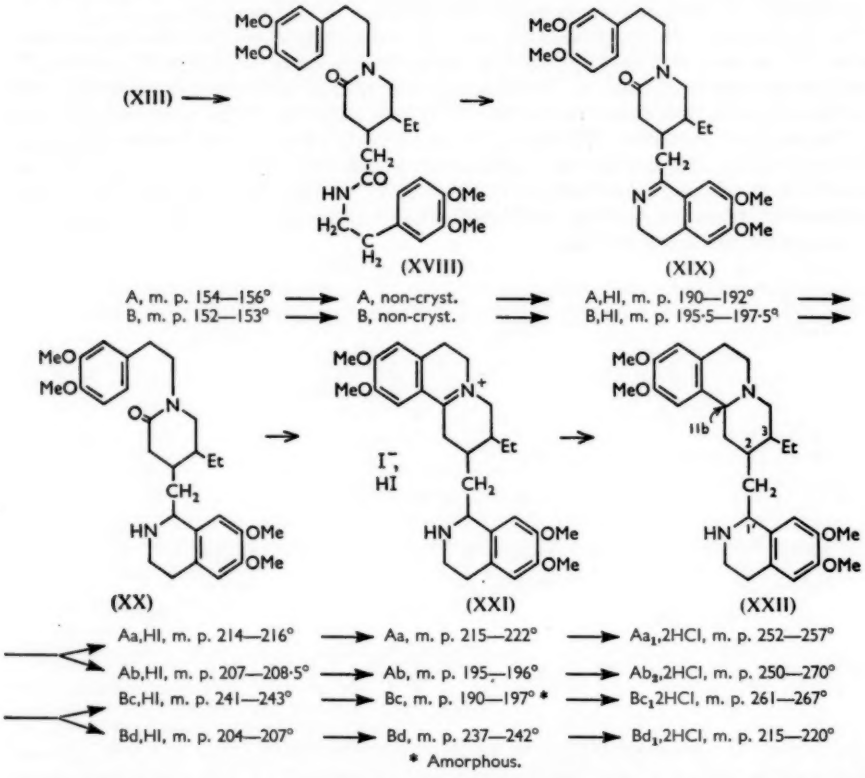


(XVII)

Condensing the pyridone (III) with 3,4-dimethoxyphenethyl iodide in t-butyl alcohol with potassium hydroxide gave the *N*-substituted pyridone (X). This with ethyl oxalate gave the potassio-salt of the pyruvic ester which with dilute acid gave the ester [15] (XI). It was assumed that only the active 4-methyl group would participitate in this reaction. Oxidation of the ester (XI) or the potassio-salt with alkaline hydrogen peroxide gave the corresponding acetic acid (XII) which, on melting, is decarboxylated to the pyridone (X).

[13] Seide, *Ber.*, 1924, **57**, 1805.
[14] Bradlow and Vanderwerf, *J. Org. Chem.*, 1951, **16**, 73.
[15] Cf. Adams and Schrecker, *J. Amer. Chem. Soc.*, 1949, **71**, 1186; and Part III.

Hydrogenation of the acetic acid (XII) with Adams catalyst gave the two stereoisomeric 2-piperidone acids (XIII), A, m. p. 154—156° (70%), and B, m. p. 152—153° (15%); a mixed m. p. between the two gave a strong depression. It was later shown [16] that the A series has the *trans*- and the B series the *cis*-configuration. Ban [5] later described a synthesis of the acids (XIII) (non-crystalline) which appeared more convenient than the above route. The Mannich base (XIV; R = H, R′ = CO_2H) was decarboxylated to give the monocarboxylic acid (XIV; R = R′ = H), now obtained crystalline, and esterified (R = Et). Treatment with ethoxycarbonylacetyl chloride yielded the diester (XV) which was converted into the ketone (XVI) and then crystallised as a monoethanol solvate. However, several attempts to repeat the condensation of the ketone (XVI) with ethyl cyanoacetate and subsequent transformations under Ban's conditions [5] gave only a trace of crystalline acid (XIII; A). However, condensing the ketone (XVI) with cyanoacetic acid gave a good yield of mixed unsaturated nitriles (XVII), which on esterification, reduction, and hydrolysis gave the two crystalline acids (XIII) A (56%) and B (12%) in good overall yield.



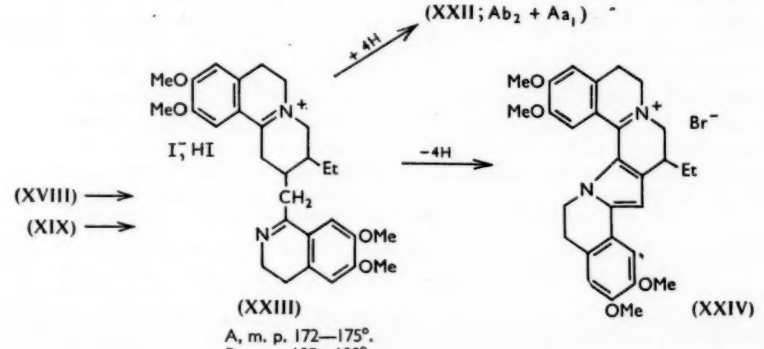
Treatment of the separated acids (XIII) A and B with triethylamine and ethyl chloroformate gave the corresponding ethoxyformic anhydrides, which with 3,4-dimethoxyphenethylamine afforded the amides (XVIII, A and B). It has already been shown [17] that cyclisation of *NN*′-bis-(3,4-dimethoxyphenethyl)glutardiamide with phosphoric oxide

[16] Brossi, Cohen, Osbond, Plattner, Schnider, and Wickens, *Chem. and Ind.*, 1958, 491; Part V, following paper.
[17] Osbond, *J.*, 1951, 3464.

in toluene resulted in γ-(3,4-dihydro-6,7-dimethoxy-1-isoquinolyl)-*N*-(2-3,4-dimethoxyphenethyl)butyramide as well as 1,3-bis-(3,4-dihydro-6,7-dimethoxy-1-isoquinolyl)propane. Application of this method to the two amides (XVIII) resulted in good yields of the monocyclised dihydroisoquinolines (XIX), isolated as their hydriodides: it will be shown later that the possible alternative cyclisation involving the piperidone did not occur. The structure of compound (XIX) was confirmed by cyclising isomer A further with phosphorus oxychloride to the benzo[*a*]quinolizinium salt (XXIII A) (see below). Hydrogenation of compound (XIX) was effected with Adams catalyst in methanol or dilute acid, or with Raney nickel or sodium borohydride. Isomer (XIX A) gave a mixture of products (XX; Aa, 55% and Ab, 45%); similarly, the isomer (XIX B) gave more (XX; Bc, 55%) than (XX; Bd, 26%).

The hydriodides of bases (XX) were cyclised by phosphorus oxychloride in chloroform and toluene in uniformly high yield.

The final step involves reduction of the dehydroemetinium salts (XXI) at the 11b centre either catalytically (Adams) or with potassium borohydride. Each dehydroemetinium salt (XXI) yielded essentially only one stereoisomer of emetine, isolated as their dihydrochlorides which were the most suitable for biological testing. *E.g.*, the salt (XXI; Aa) gave the emetine isomer (XXII; Aa_1) in 80% yield. Two isomers are theoretically possible in these reductions and in some cases a very small amount of a second compound was detected. *E.g.*, in addition to (XXII; Aa_1), 5—10% of a non-crystalline material considered to be (XXII; Aa_2) was found by paper chromatography and isolated; however, its structure was not established with certainty. In order to ensure homogeneity of the isomers (XXII) and to detect (±)-emetine, paper chromatography was employed extensively. By this means all four isomers Aa_1, Ab_2, Bc_1, and Bd_1 were separated and only one (XXII; Aa_1) could not be separated from emetine (see Table 1). This most abundant isomer (XXII; Aa_1) was considered to be (±)-emetine on the following evidence. The melting points of the base, dihydrochloride, and dihydriodide were in close agreement with those of authentic optically active specimens, and infrared comparison showed no differences except in the case of the dihydrochloride. The dihydrochloride of (±)-Aa_1, when tested against *E. histolytica* in weanling rats by a modification of the Jones [18] method, had slightly more than half the activity of (±)-emetine dihydrochloride, and the same activity *in vitro* (see Table 1, revised values [11]). It should be noted that the other stereoisomers of emetine (XXII; Ab_2, Bc_1, and Bd_1) do



not approach this high level of amœbicidal activity *in vivo* and cannot be considered to be (±)-emetine, in conformity with their chromatographic behaviour. Resolution of isomer

[18] Jones, *Ann. Trop. Med. Parasitol.*, 1956, **40**, 130.

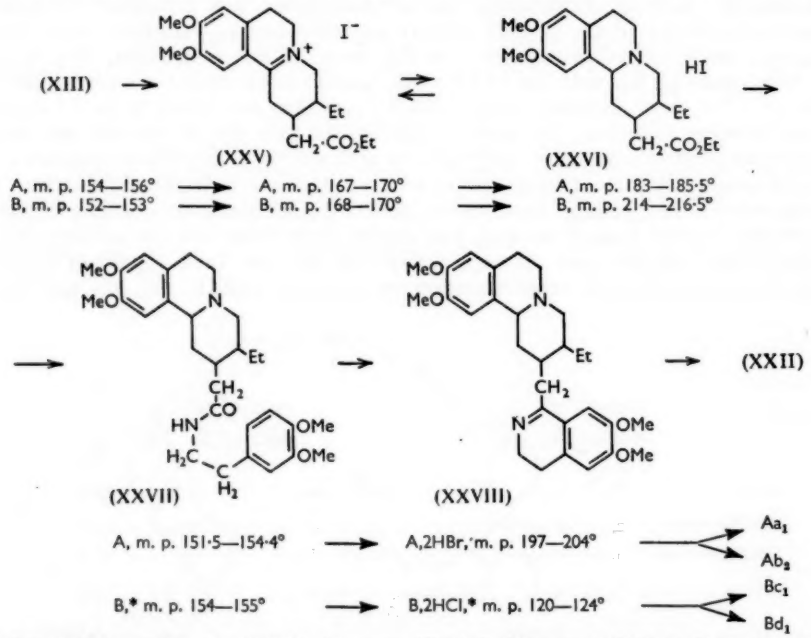
(XXII; Aa_1) with two mols. of (+)-dibenzoyltartaric acid gave the bis-(−)-dibenzoyltartrate of (Aa_1), which was identical with an authentic specimen prepared by Dr. Brossi [19] as shown by m. p., mixed m. p., paper chromatography, infrared spectra, and rotation. From the synthetic bis-(−)-dibenzoyltartrate, the (+)-dihydrochloride and (+)-dihydriodide were prepared, and again comparison with authentic specimens showed no differences (see p. 3541). It follows if compound (XXII; Aa_1) is (±)-emetine, then isomer (XXII; Ab_2) is isoemetine as this isomer is epimeric with emetine at position 1'.

TABLE 1.

Stereoisomer of emetine,2HCl	Amœbicidal *in vivo* test: CD_{50} (mg./kg.)	Amœbicidal *in vitro* test: m.c. (g./ml.)	R_F (emetine = 1) *
Aa_1	6·25	10	1·00
Ab_2	64·6	10,000	0·62 †
Bc_1	133	1000	0·79 †
Bd_1	200	1000	0·67 †
(+)-Emetine,2HCl	6·25—12·5, 4—8	10—100	1·00

* These values are: Distance travelled by substance/Distance travelled by emetine, in ethyl methyl ketone–2N-aqueous hydrochloric acid on Whatman No. 1 paper.
† Separation from emetine can be effected.

The above work located (±)-emetine as being in the A series; in addition, the paper-chromatographic, physical, and biological properties of compound (XXII; Aa_1) in relation to the other isomers allowed a second approach to be made, namely, the simultaneous



* The transformation of (XXVI; B) ⟶ (XXVII; B) ⟶ (XXVIII; B) ⟶ emetine isomers (XXII; Bc_1) and (Bd_1) was carried out by Brossi and Schnider.[19] Their compounds have been included in the above chart for completeness. The conditions used by Brossi and Schnider for the above reactions were used by us in the corresponding A series.

reduction of the two double bonds in tetradehydroemetine (cf. XXIII; A). Cyclisation of the amide (XVIII; A) to give a pentacyclic base (XXIII; A) was best effected with phosphorus oxychloride alone; alternatively, cyclisation of the base (XIX; A) gave the

same iodide hydriodide A of (XXIII). Similarly, the isomeric amide (XVIII; B) gave the quaternary salt B of (XXIII). Dehydrogenation of a salt of (XXIII; A) with mercuric acetate, etc., gave (±)-rubremetinium bromide (XXIV) in good yield, and comparison with an authentic specimen showed them to be identical. Catalytic reduction (Adams) of the chloride hydrochloride derived from (XXIII; A) gave (±)-isoemetine (XXII; Ab_2) (in 60% yield), identified by the R_F value, infrared spectrum, and amœbicidal activity *in vivo*. The mother-liquor gave mixtures of (±)-isoemetine (Ab_2) and (±)-emetine (Aa_1), as shown by paper chromatography, but the small quantities present did not allow us to obtain pure (±)-emetine by this route. Openshaw and Wood [20] showed that catalytic reduction of a tetradehydroemetine salt, probably as (XXIII),[20,21] gave only isoemetine. Reduction with other catalysts under various conditions and with potassium borohydride in methanol gave substantially the same result. Catalytic reduction of an isomeric chloride hydrochloride (cf. XXIII; B) gave rise almost certainly to the emetine isomer (XXII; Bc) as shown by the melting point and paper chromatography, but this was not firmly established. Evstigneeva and her co-workers [8] obtained a salt (XXIII) (m. p. 257—258°; A or B?) by a different route which on hydrogenation (Adams) gave an isomer considered to be (±)-emetine, together with a second isomer.

A third approach to the synthesis of stereoisomers of emetine was carried out as shown in the flow sheet above. Esterification of the acids (XIII; A and B) gave the corresponding esters, which without isolation were cyclised to give the quaternary iodides (XXV; A and B). These on catalytic reduction (Adams) gave in each case only one isomer, isolated as their hydriodides (XXVI) in 91 and 95% yield respectively. In the case of salt (XXV; A) many experiments were carried out with different catalysts under varying conditions and by chemical reduction, such as potassium borohydride, alkaline sodium dithionite,[22] formic acid on the anhydro-base,[23] in an attempt to obtain the other isomer, but in all cases only the isomer (XXVI; A) was obtained; zinc and hydrochloric acid [24] gave no crystalline material. Treatment of salts (XXVI; A and B) with mercuric acetate gave the dehydro-esters (XXV; A and B) in high yield.

Condensing of the amino-acid corresponding to (XXVI; A) with 3,4-dimethoxyphenethylamine gave the amide (XXVII; A). Brossi and Schnider [19] later obtained the amide (XXVII; A) from 3-ethyl-1,2,3,4,5,6-hexahydro-9,10-dimethoxy-2-oxo-11b*H*-benzo[*a*]quinolizine,[4,25] identity being provided by m. p., mixed m. p., and infrared-spectral comparison. The hydriodide, m. p. 227—228°, of base (XXVII; A) was not identical with either hydriodide of base (XX; Aa or Ab), and this confirms the view that in our first synthesis the direction of monocyclisation was (XVIII) ⟶ (XIX). Cyclisation of the base (XXVII; A) with phosphorus oxychloride gave (±)-*O*-methylpsychotrine dihydrobromide (XXVIII; A) which on hydrogenation (Adams) led to approximately equal amounts of compounds (XXII; Ab_2) [(±)-isoemetine] and (XXII; Aa_1) [(±)-emetine] (45, 40%), whose identities were established by m. p.s, mixed m. p.s, paper chromatography, and infrared-spectral comparison. Preobrazhenskii and his co-workers [7] and Battersby and Turner [10] described the isolation of emetine by this route. Both groups were using the *trans*-isomer (XXVII) which corresponds to our A series [16] (cf. van Tamelen and his co-workers [26]).

During this work Brossi and Schnider [19] prepared an acid corresponding to (XXVI) by

[19] Brossi, Schnider *et al.*, unpublished work.
[20] Openshaw and Wood, *J.*, 1952, 391.
[21] Battersby and Openshaw, *J.*, 1949, S67; Hazlett and McEwen, *J. Amer. Chem. Soc.*, 1951, **73**, 2578; Tietz and McEwen, *ibid.*, 1953, **75**, 4945.
[22] Sugasawa, Akahoshi, and Suzuki, *J. Pharm. Soc. Japan*, 1952, **72**, 1273.
[23] De Benneville and Macartney, *J. Amer. Chem. Soc.*, 1950, **72**, 3073; Leonard, Thomas, and Gash, *ibid.*, 1955, **77**, 1556.
[24] Weisenborn and Diassi, *ibid.*, 1956, **78**, 2022; Klohs, Keller, Williams, and Kusserow, *ibid.*, 1957, **79**, 3763.
[25] Brossi, Lindlar, Walter, and Schnider, *Helv. Chim. Acta*, 1957, **41**, 119.
[26] van Tamelen, Aldrich, and Hester, *J. Amer. Chem. Soc.*, 1957, **79**, 4817.

XUM

a different route. Esterification and examination of the hydriodide by m. p., mixed m. p., and infrared spectroscopy showed it to be identical with our salt (XXVI; B). They had already transformed this by way of (XXVII; B) and (XXVIII; B) into two emetine isomers (XXII) which were shown to be identical with our emetine stereoisomers (XXII; Bc_1 and Bd_1) by paper chromatography, infrared-spectral comparison, m. p.s, mixed m. p.s, and amœbicidal activity *in vivo*.

Experimental

5-Ethyl-4-methyl-2-pyridone (III) *and 3-Ethyl-4-methyl-2-pyridone* (IV).—(*a*) Sodamide (from sodium, 5·75 g.), dimethylaniline (22·5 c.c.), and β-collidine (24·2 g.) were heated at 170° for 5 hr., then cooled. Methanol, water, and sodium hydroxide solution were added and the mixture was extracted 6 times with chloroform. The basic material was distilled (b. p. 80—100°/0·7 mm.) to give an oil (11·35 g., 42%), n_D 1·5562, which was a mixture of 5-ethyl-4-methyl-2- and -6-aminopyridine. The mixture (10·8 g., 0·079 mole) was dissolved in 2N-sulphuric acid. Sodium nitrite (0·079 mole) in water (10 c.c.) was slowly added at 5°, and the whole warmed to 90° for 0·5 hr., made alkaline, and taken to dryness under reduced pressure. Extraction with ethanol yielded on distillation a mixture of pyridones (8·2 g., 75%), b. p. 150—158°/0·9 mm. The *3-ethyl-4-methyl-2-pyridone*, which was predominant, crystallised from ethyl acetate as plates, m. p. 169·5—172° (Found: C, 70·25; H, 8·2; N, 10·3. $C_8H_{11}ON$ requires C, 70·1; H, 8·1; N, 10·2%), $\lambda_{max.}$ (in H_2O) 230 (log ε 3·67), 293 mμ (log ε 3·83). After crystallisation from ethyl acetate the required *5-ethyl-4-methyl-2-pyridone*, m. p. 160·5—161·5°, was obtained in low yield as prisms (Found: C, 70·4; H, 7·9; N, 10·65%), $\lambda_{max.}$ (in H_2O) 230 (log ε 3·81), 298 (log ε 3·77).

(*b*) (i) To a solution of sodium (2·54 g.) in dry benzyl alcohol (90 c.c.) was added 2,6-dichloro-5-ethyl-4-methylpyridine [12] (18·9 g.). The solution was heated on a boiling-water bath for 9 hr., then under reflux for 0·75 hr. The benzyl alcohol was removed, water was added, the whole was extracted with ether, and the extract was washed with water and dried (K_2CO_3). Two distillations gave essentially *6-benzyloxy-2-chloro-3-ethyl-4-methylpyridine* (VII; R = CH_2Ph) (23·07 g., 88%), b. p. 150°/0·6 mm., n_D^{20} 1·5680 contaminated with a certain amount of the other isomer (Found: C, 69·3; H, 6·1; N, 5·4; Cl, 13·1. $C_{15}H_{16}ONCl$ requires C, 68·85; H, 6·2; N, 5·35; Cl, 13·45%).

This base (2·5 g.) was hydrogenated (palladium–charcoal) in methanol at room temperature and atmospheric pressure, yielding essentially the hydrochloride (0·9 g.), m. p. 161—168°, of 5-ethyl-4-methyl-2-pyridone. This salt yielded a base whence crystallisation from ethyl acetate afforded pure 5-ethyl-4-methyl-2-pyridone as prisms, m. p. 160—162°, identical with that prepared by method (a), together with a small amount of the 3-ethyl-4-methyl-2-pyridone.

(ii) Potassium (8·6 g.) was refluxed with diphenylmethanol (55·2 g.) in xylene (400 c.c.) in a nitrogen atmosphere for 20 hr. 2,6-Dichloro-3-ethyl-4-methylpyridine (38 g.) was then added and refluxing continued for a further 24 hr. The xylene was washed with water and evaporated to dryness under reduced pressure. The residue was crystallised twice from methanol, to give *2-chloro-6-diphenylmethoxy-3-ethyl-4-methylpyridine* (VII; R = $CHPh_2$) (26·1 g.), m. p. 104—105° (Found: C, 75·2; H, 5·95; N, 4·2; Cl, 10·3. $C_{21}H_{20}ONCl$ requires C, 74·7; H, 6·0; N, 4·15; Cl, 10·5%). The other isomer, *6-chloro-2-diphenylmethoxy-3-ethyl-4-methylpyridine* was isolated in small amount from the mother-liquor and after crystallisation from methanol had m. p. 94—95° (Found: C, 74·0; H, 5·8; N, 4·0%). The 2-chloro-ether (26·1 g.) in ethanol (600 c.c.) and water (10 c.c.) containing sodium acetate (14 g.) was hydrogenated (3 g. of palladium–charcoal) at room temperature and atmospheric pressure. This yielded the 5-ethyl-4-methyl-2-pyridone (8·57 g.), m. p. 160—161°. In a similar way the other isomer yielded on hydrogenolysis the 3-ethyl-4-methyl-2-pyridone.

(*c*) 2,6-Dichloro-3-ethyl-4-methylpyridine (19 g.) in dry xylene (100 c.c.) was added to sodium isopropoxide [from sodium (2·3 g.) in propan-2-ol (75 c.c.)] suspended in xylene (100 c.c.) and refluxed for 16 hr. The solution was filtered and the product distilled, to give essentially *2-chloro-3-ethyl-6-isopropoxy-4-methylpyridine* (VII; R = Pr^i) (17·77 g.), b. p. 78—80°/0·8 mm., n_D 1·5075, contaminated with the other isomer (Found: C, 61·5; H, 7·7; N, 6·45; Cl, 16·6. $C_{11}H_{16}ONCl$ requires C, 61·8; H, 7·55; N, 6·6; Cl, 16·6%).

(*c'*) The above chloro-isopropoxypyridine (15·4 g.) in methanol (150 c.c.) was hydrogenated in the presence of palladised charcoal (4 g.) and sodium acetate (12 g.) at room temperature and atmospheric pressure. The *5-ethyl-2-isopropoxy-4-methylpyridine* (IX; R = Pr^{i}) (14·73 g.), b. p. 132—134°/7·2 mm., was distilled (Found: C, 73·8; H, 9·8; N, 7·55. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·6; N, 7·8%). This product (2·4 g.) was heated with concentrated hydrochloric acid (15 c.c.) in a sealed tube at 118° for 4·5 hr. The resulting 5-ethyl-4-methylpyridone was extracted with chloroform and crystallised from ethyl acetate as prisms (47%), m. p. 159·5—162°. From the mother-liquor 9% of the isomeric pyridone was obtained.

(*c''*) Crude 2-chloro-3-ethyl-6-isopropoxy-4-methylpyridine (42 g.) was refluxed in 48% hydrobromic acid (400 c.c.) for 0·5 hr. Hydrobromic acid was removed, and the solution was made slightly alkaline with aqueous sodium carbonate. The solid that separated crystallised from ethyl acetate and then alcohol, to give *6-chloro-5-ethyl-4-methyl-2-pyridone* (9·47 g.), m. p. 174—176° (Found: C, 55·9; H, 5·4; N, 7·8; Cl, 20·8. $C_8H_{10}ONCl$ requires C, 56·0; H, 5·9; N, 8·2; Cl, 20·7%).

The above 6-chloro-2-pyridone (1·55 g.) in methanol (25 c.c.) was hydrogenated at room temperature and atmospheric pressure in the presence of sodium acetate (1·5 g.) and palladised charcoal (1 g.), yielding 5-ethyl-4-methyl-2-pyridone (0·75 g.), m. p. 159—161°, identical with that obtained above.

3-Methyl-2-pyridone.—Sodium nitrite (3·7 g.) in water (10 c.c.) was added to 2-amino-3-methylpyridine (5·0 g.) in sulphuric acid (concentrated acid 5·5 c.c., in water, 42 c.c.) at 5°. After 1 hr. at 10° the solution was heated at 90° for 1 hr. Potassium carbonate was added, and the solution concentrated to dryness. The residue was extracted with boiling ethanol. The ethanol extracts were combined, evaporated, and sublimed at 100°/0·5 mm. to give the pyridone (2·7 g.), which on crystallisation from benzene had m. p. 141—143° (Seide [13] gives m. p. 140°), $\lambda_{max.}$ (in H_2O) 226 (log ε 3·84), 295 mμ (log ε 3·93).

5-Methyl-2-pyridone.—This *isomer* (2·9 g.) was prepared similarly from 2-amino-5-methylpyridine (5 g.) and after sublimation at 110°/1·0 mm. and crystallisation from benzene had m. p. 184—188° (Found: C, 66·0; H, 6·5; N, 12·8. C_6H_7ON requires C, 66·1; H, 6·5; N, 12·8%), $\lambda_{max.}$ (in H_2O) 227 (log ε 3·91); 303 mμ (log ε 3·79).

1-(3,4-Dimethoxyphenethyl)-5-ethyl-4-methyl-2-pyridone (X).—5-Ethyl-4-methyl-2-pyridone (2·72 g.) was added to a solution of potassium hydroxide (1·32 g.) in water (1 c.c.) and t-butyl alcohol (80 c.c.), followed by 3,4-dimethoxyphenethyl iodide (5·84 g.), and the solution was refluxed for 4 hr. The butanol was removed, water added, the whole extracted 3 times with benzene, the extracts were washed with water, and the product converted into the *hydrochloride* (4·28 g.), m. p. 199—201·5° (decomp.) (Found: C, 64·2; H, 7·3; N, 4·0; Cl, 10·5. $C_{18}H_{23}O_3N$,HCl requires C, 64·5; H, 7·2; N, 4·15; Cl, 10·5%).

The *pyridone*, obtained from the hydrochloride separated from ethyl acetate–ether as prisms, m. p. 72—75·5° (Found: N, 4·7. $C_{18}H_{23}O_3N$ requires N, 4·65%).

Ethyl 1-(3,4-Dimethoxyphenethyl)-5-ethyl-1,2-dihydro-2-oxo-4-pyridylpyruvate (XI).—Absolute ethanol (2·85 c.c.) was added dropwise to potassium (0·43 g.) under dry ether (10 c.c.), followed by ethyl oxalate (1·6 g.) in ether (6 c.c.) at 0°. The pyridone (X) (3·01 g.) in dry benzene (40 c.c.) and ether (140 c.c.) was added and the solution refluxed for 24 hr. After cooling to 0° for 4 hr. the yellow potassio-salt (3·01 g., 85% based on pyridone used) was filtered off and washed with ether. Treatment of this salt with 2N-sulphuric acid, extraction with chloroform, and crystallisation from ethyl acetate gave the *ester*, m. p. 141·5—142·5° (Found: C, 65·7; H, 7·0; N, 3·4. $C_{23}H_{27}O_6N$ requires C, 65·8; H, 6·8; N, 3·5%).

The potassio-salt of the pyruvate (3 g.) in 10% aqueous sodium hydroxide (12·4 c.c.) was kept at 0° for 18 hr. A small amount of ice was added, followed by 30% hydrogen peroxide (2·41 c.c.); after 24 hr. at 0° a further quantity of hydrogen peroxide (1·03 c.c.) was added. After a further 24 hr. at 0° manganese dioxide (0·1 g.) was added, the mixture was filtered, and the filtrate made slightly acid with hydrochloric acid and extracted with chloroform. Treatment of the product with ethereal hydrogen chloride gave the *acetic acid hydrochloride* (cf. XII) which crystallised from methanol–ether as prisms (1·92 g., 76·5%), m. p. 160·5—162·5° (decomp.) (Found: C, 59·3; H, 6·7; H, 3·3. $C_{19}H_{23}O_5N$,HCl requires C, 59·8; H, 6·3; N, 3·7%). The free *acid* (obtained from the hydrochloride) and crystallised from methanol had m. p. 154° (decomp.) (Found: N, 4·2. $C_{19}H_{23}O_5N$ requires N, 4·1%), $\lambda_{max.}$ (in 2N-HCl) 228, 285, and 303 mμ (log ε 3·99, 3·68, and 3·71 respectively).

1-(3,4-Dimethoxyphenethyl)-5-ethyl-2,4-dioxopiperidine (XVI).—The 2,4-dioxopiperidine was

XUM

prepared by Ban's method [5] with some improvement of yield and crystallisation of intermediates. 3,4-Dimethoxyphenethylamine was condensed with formaldehyde and ethylmalonic acid to give the Mannich base, m. p. 157—158°. Decarboxylation was then effected in 60% acetic acid to give α-(3,4-dimethoxyphenethylaminomethyl)butyric acid, m. p. 155—156° (Found: C, 64·1; H, 8·2; N, 4·9. Calc. for $C_{15}H_{23}O_4N$: C, 64·2; H, 8·2; N, 4·9%), the overall yield for the two steps being 75%. Esterification of the acid with ethanol and hydrogen chloride, followed by treatment with the acid chloride of ethyl hydrogen malonate gave ethyl α-[*N*-(ethoxycarbonylacetyl)-*N*-(3,4-dimethoxyphenethyl)aminomethyl]butyrate. Dieckmann cyclisation, by sodium in xylene, of the diester, hydrolysis by 10% acetic acid, and decarboxylation gave the ketone as a crystalline *ethanol solvate*, m. p. 38—40°, in 62% overall yield (Found: C, 65·3; H, 8·1; N, 4·2. $C_{17}H_{23}O_4N,C_2H_5{\cdot}OH$ requires C, 64·95; H, 8·3; N, 4·0%).

1-(3,4-*Dimethoxyphenethyl*)-5-*ethyl*-1,2-*dihydro*-2-*oxo*-4-*piperidylacetic Acids* (XIIIA *and* B).—(i) 1-(3,4-Dimethoxyphenethyl)-5-ethyl-1,2-dihydro-2-oxo-4-pyridylacetic acid (6·91 g.) was hydrogenated in methanol (400 c.c.) in the presence of Adams catalyst (0·3 g.) at room temperature and atmospheric pressure. After 2—3 days the slow uptake of hydrogen ceased (*ca.* 2 mol.). The *acetic acid* (A) separated from methanol as prisms (4·56 g., 70%), m. p. 154—156° (Found: C, 65·2; H, 8·35; N, 4·5. $C_{19}H_{27}O_5N$ requires C, 65·3; H, 7·8; N, 4·0%).

From the mother-liquor, on concentration, the *acid* (B) separated as prisms (0·94 g., 14%), m. p. 152—153°. A mixed m. p. between A and B gave a marked depression (m. p. 130—135°) (Found: C, 65·3; H, 7·9; N, 3·9. $C_{19}H_{27}O_5N$ requires C, 65·3; H, 7·8; N, 4·0%).

(ii) 1-(3,4-Dimethoxyphenethyl)-5-ethyl-2,4-dioxopiperidine ethanol solvate (70·3 g., 0·2 mole), dry cyanoacetic acid (39 g., 0·459 mole), dry ammonium acetate (5 g.), and glacial acetic acid (5 ml.) were dissolved in benzene (500 ml.) and refluxed in a Dean and Stark apparatus at 110° for 3 hr. Cyanoacetic acid (12 g., 0·141 mole), ammonium acetate (3 g.), and glacial acetic acid (5 ml.) were added and the whole was refluxed for a further 4 hr. Ammonium acetate (3 g.) was added and the mixture refluxed for a further 6 hr., then the bath-temperature was raised to 120°, the benzene distilling. The residual syrup was heated in the bath for a further 12 hr. at 120°, dissolved in benzene (200 ml.), washed 3 times with 2N-sodium carbonate, then with water, dried (Na_2SO_4), and evaporated. The mixture of unsaturated nitriles (XVII) (80 g.) was dissolved in absolute alcohol (600 ml.), saturated with hydrogen chloride at 0°, and refluxed for 2½ hr. with continued passage of hydrogen chloride. The alcohol was removed and water (*ca.* 300 ml.) added. The solution was extracted 3 times with benzene, washed twice with 2N-sodium carbonate, and dried (Na_2SO_4). The benzene was removed, and the resulting ethyl esters (75 g.) were hydrogenated in methanol (650 ml.) at room temperature and atmospheric pressure in the presence of Adams catalyst (0·5 g.) (uptake 4·4 l.) (theor. 4·9 l.). The catalyst was removed, and the solution was concentrated to *ca.* 600 ml., treated with potassium hydroxide (20·7 g.) in water (20 c.c.), and refluxed for 3½ hr.; water was then added and the methanol removed under reduced pressure. The aqueous solution was acidified, extracted 3 times with chloroform, dried (Na_2SO_4), and co-distilled twice with methanol; the residue was dissolved in methanol (300 ml.) and the first main crop was the almost pure acetic acid A. Fractional crystallisation of the mother-liquor gave a total amount of the pure A isomer, m. p. 154—156° [identical with A prepared as in (i)] (39·49 g., 56·5%). The isomer (B), m. p. 152—153° (8·34 g., 12%), was identical with the B isomer prepared in experiment (i). When the original Ban process [5] was attempted the gummy mixture of acids at the end yielded only a trace of acetic acid A after being seeded with our crystalline material.

N-(3,4-*Dimethoxyphenethyl*)-α-[1-(3,4-*dimethoxyphenethyl*)-5-*ethyl*-2-*oxo*-4-*piperidyl*]*acetamide* (XVIII; A *and* B).—The acetic acid (XIII; A) (2·79 g.) was treated in dry dimethylformamide (25 c.c.) at 0° with triethylamine (0·85 g.), followed by ethyl chloroformate (1·12 g.) in dry dioxan (4 c.c.) at −30° during 10 min. The mixture was kept at −30° for a further 5 min. and at −10° for 10 min. Then 3,4-dimethoxyphenethylamine (1·6 g.) and triethylamine (0·85 g.) in dimethylformamide (20 c.c.) were added during 10 min. with stirring, and the mixture was kept at room temperature overnight. The solution was concentrated to a thick syrup, dissolved in chloroform, and washed with 2N-hydrochloric acid, 2N-sodium carbonate, and water and dried (Na_2SO_4). This yielded a pale yellow gum (quantitative yield) which did not crystallise. In a similar way the acetic acid (XIII; B) was also converted into the amide (XVIII; B). Compounds of similar structure have been prepared by a different route by Evstigneeva *et al.*,[7] also non-crystalline.

4-(3,4-Dihydro-6,7-dimethoxy-1-isoquinolylmethyl)-1-(3,4-dimethoxyphenethyl)-5-ethyl-2-piperidone Hydriodides (cf. XIX; A *and* B).—The amide (XVIII; A) [prepared from the corresponding acetic acid (XIII; A) (5·28 g.)] was treated in dry refluxing toluene (140 c.c.) with phosphoric oxide (50 g.) for ¾ hr. Further oxide (50 g.) was added and refluxing continued for a further 1¼ hr. The toluene was decanted and the residual material added to ice. The solution was extracted with ether, and aqueous potassium iodide was added. The *hydriodide* was extracted three times with chloroform, dried, and evaporated. The residue crystallised from methanol–ethyl acetate as yellow prisms [8·05 g.; 85% for the two steps from (XIII; A)], m. p. 190—192° (Found: C, 56·15; H, 6·5; N, 4·5. $C_{29}H_{38}O_5N_2$,HI requires C, 56·0; H, 6·3; N, 4·5%). $\lambda_{max.}$ (in H_2O) 230, 287 sh, 303, and 354 mμ (log ε 4·44, 3·81, 3·96, and 3·95 respectively). The *base* crystallised from ethyl acetate as pale yellow prisms, m. p. 122·5—124° (Found: C, 70·2; H, 7·8; N, 5·35. $C_{29}H_{38}O_5N_2$ requires C, 70·4; H, 7·7; N, 5·7%).

A similar result was obtained by using polyphosphoric acid instead of phosphoric oxide, although the yield was lower.

Similarly the amide (XVIII; B) was cyclised to give the corresponding *hydriodide*, m. p. 195·5—197·5°, as yellow prisms (from methanol–ethyl acetate) [76% yield (from XIII; B)] [mixed m. p. with (XIX; A) 187—189°] (Found: C, 56·25; H, 6·2; H, 4·3%].

1-(3 : 4-Dimethoxyphenethyl)-5-ethyl-4-(1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolylmethyl)-2-piperidone Hydriodides [XX; Aa, Ab, (Bc), *and* (Bd)].—The hydriodide (5·0 g.) of base (XIX; A) was hydrogenated in methanol (75 c.c.) with Adams catalyst (0·1 g.) at room temperature and atmospheric pressure until one mol. had been absorbed. The solution was filtered and concentrated; on cooling, the *hydriodide* (cf. XX; Aa) separated as colourless prisms (2·6 g., 51·8%), m. p. 214—216° (Found: C, 55·5; H, 6·6; N, 4·4. $C_{29}H_{40}O_5N_2$,HI requires C, 55·8; H, 6·6; N, 4·5%), $\lambda_{max.}$ (in H_2O) 226 and 280 mμ (log ε 4·43 and 3·74). On concentration the second *hydriodide* (cf. XX; Ab) was obtained which after two recrystallisations separated from methanol–ether as pale yellow plates (2·05 g., 41%), m. p. 207—208·5° [mixed m. p. between (Aa) and (Ab) 203—208°] (Found: C, 56·3; H, 6·6; N, 4·5; I, 20·9%).

The amide hydriodide (cf. XIX; B) (4·26 g.) was reduced with potassium borohydride (1·0 g.) in methanol (100 c.c.) at room temperature to give two stereoisomers (XX; Bc and Bd). The hydriodide (cf. XX; Bc) (2·02 g., 55%) separated from methanol, in which it was sparingly soluble, as yellow plates, m. p. 244—246°. Catalytic reduction with Adams catalyst in methanol raised the amount to 82% (Found: C, 55·6; H, 6·8; N, 4·8%). From the mother-liquor of the potassium borohydride reduction, the epimer (XX; Bd) was isolated as the *hydriodide* after several crystallisations from methanol–ether as pale yellow clumps (1·21 g., 26%), m. p. 203—205° (Found: C, 56·3; H, 7·0; N, 4·7%).

3-Ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxy-2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolylmethyl)benzo[a]*quinolizinium Iodide Hydriodides* (cf. XXI; Aa, Ab, Bc, and Bd).—The reduced hydriodide (cf. XX, Aa) (4·0 g.) was dissolved in dry chloroform (40 c.c.) of which 5 c.c. were removed by distillation. Dry toluene (30 c.c.) and phosphorus oxychloride (14 c.c.) were added and the solution was refluxed on a water-bath for 0·5 hr. The reagents were removed and the resulting red gum was dissolved in hot water (4 extractions) to which potassium iodide was added and the *iodide hydriodide* was extracted with chloroform and crystallised from methanol as yellow prisms (3·8 g., 81%), m. p. 215—222° (decomp.) (Found: C, 47·9; H, 5·4; N, 3·7. $C_{29}H_{39}O_4N_2I$,HI requires C, 47·4; H, 5·5; N, 3·8%).

The reduced hydriodide (cf. XX; Ab) (2·4 g.) was cyclised in a similar way. The resulting *iodide hydriodide* separated as yellow prisms, m. p. 195—196° (2·25 g., 79%) (Found: C, 47·2; H, 5·7; N, 3·6%). An air-dried sample had m. p. 186—193° with softening at 180° (Found: C, 45·9; H, 5·7; N, 3·8; I, 34·0; H_2O, 4·1. $C_{29}H_{39}O_4N_2I$,HI,1·5H_2O requires C, 45·7; H, 5·7; N, 3·6; I, 33·3; H_2O, 3·5%), $\lambda_{max.}$ (in H_2O) 227, 290, 302·5, and 350 mμ (log ε 4·7, 3·8, 3·88, and 3·9).

The *isomer* (XXI; Bc) was obtained in a similar manner in good yield but did not crystallise. The amorphous salt separated from ethanol as a yellow solid, m. p. 190—197° (Found: C, 46·3; H, 5·1; N, 3·9; I, 34·6. $C_{29}H_{39}O_4N_2I$,HI,0·5H_2O requires C, 46·9; H, 5·5; N, 3·8; I, 34·2%).

The *iodide hydriodide* (XXI; Bd) was obtained in 70% yield as pale yellow crystalline nodules (from ethanol), m. p. 237—242° (Found: C, 46·95; H, 5·5; N, 3·65; I, 34·1%).

2-(3,4-Dihydro-6,7-dimethoxy-1-isoquinolylmethyl)-3-ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxybenzo[a]*quinolizinium Iodide Hydriodide* (*Tetradehydroemetinium Iodide Hydriodide*) (XXIII; A).—(*a*) 1-(3,4-Dimethoxyphenethyl)-5-ethyl-1,2-dihydro-2-oxo-4-piperidylacetic acid (XIII;

XUM

A) (0·69 g.) was converted into the amide (XVIII; A), which was dissolved in phosphorus oxychloride (13 c.c.), and heated at 95° for 0·5 hr. The excess of reagent was removed and the gum, after being washed once with light petroleum, was dissolved in ethanol and water and treated with excess of potassium iodide. The *iodide hydriodide* was extracted with chloroform and crystallised from methanol as yellow prisms, m. p. 172—175° (1·10 g., 75%) (Found, in air-dried sample: C, 44·2; H, 5·95; N, 3·5; I, 33·0; loss on drying 6·0. $C_{29}H_{37}O_4N_2I,HI,2{\cdot}5H_2O$ requires C, 44·8; H, 5·6; N, 3·6; I, 32·65; $2{\cdot}5H_2O$, 5·8. Found, in dried sample: C, 48·1; H, 5·4; N, 3·7; I, 34·9. $C_{29}H_{37}O_4N_2I,HI$ requires C, 47·6; H, 5·2; N, 3·8; I, 34·65%), $\lambda_{max.}$ (in H_2O) 227, 240 sh, 305, 354 mμ (log ε 4·6, 4·52, 4·20, and 4·19).

(ii) 4-(3,4-Dihydro-6,7-dimethoxy-1-isoquinolylmethyl)-1-(3,4-dimethoxyphenethyl)-5-ethyl-2-piperidone hydriodide (cf. XIX; A) (2·0 g.) was cyclised in chloroform (10 c.c.), toluene (11 c.c.), and phosphorus oxychloride (7 c.c.) at 95° for 0·75 hr. The iodide hydriodide was obtained as described above as yellow prisms (2·07 g.; 87%), m. p. and mixed m. p. 175—177°.

The acetic acid (XIII; B) (0·69 g.) was converted into the amide (XVIII; B), as in the example above, and cyclised with phosphorus oxychloride (2 c.c.) and toluene (10 c.c.) for 15 min. The product (XXIII; B) crystallised from methanol as the sparingly soluble *iodide hydriodide* (0·36 g., 66%), m. p. 185—188°, yellow prisms (Found: C, 47·6; H, 5·75; N, 3·6; I, 34·1. $C_{29}H_{37}O_4N_2I,HI$ requires C, 47·6; H, 5·2; N, 3·8; I, 34·65%), $\lambda_{max.}$ (in H_2O) 227, 240 sh, 305, 354 mμ (log ε 4·80, 4·51, 4·20, 4·18 respectively).

2-*Ethoxycarbonylmethyl*-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Iodide* (XXV; A).—(i) 1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidylacetic acid (XIII; A) (1·05 g.; m. p. 155·5—157°) was esterified with absolute ethanol (30 c.c.) and hydrogen chloride at room temperature for 18 hr. The ethanol and hydrogen chloride were removed and the resulting ester hydrochloride was cyclised in toluene (5 c.c.) by phosphorus oxychloride (3 c.c.) at 95° for 0·5 hr. The quaternary *iodide*, prepared in the usual way, was extracted with chloroform and crystallised from ethanol–ethyl acetate with a few drops of ether, as yellow needles (1·26 g., 86%), double m. p. 135—140° and 167—170° (Found: C, 51·8; H, 6·0; N, 2·9; I, 26·4. $C_{21}H_{30}O_4NI$ requires C, 51·75; H, 6·2; N, 2·9; I, 26·0%), $\lambda_{max.}$ (in H_2O) 235, 302, and 348 mμ (log ε 4·34, 4·0, and 4·1).

(ii) The hydriodide (XXVI; A) (1·2 g.) was treated in methanol (5 c.c.) with excess of 2N-sodium carbonate, and the base extracted with ether, recovered, and heated in glacial acetic acid (30 c.c.) with mercuric acetate (2·4 g.) at 60° for 2·5 hr. Mercurous acetate separated after 10 min. The solution was cooled, diluted with water, and filtered. The filtrate was treated with hydrogen sulphide, the metal sulphide was filtered off, and the filtrate concentrated to 50 c.c. and acidified with hydrochloric acid. Potassium iodide was added and the quaternary iodide ester was extracted with chloroform and crystallised from methanol–ether as yellow plates (0·94 g., 78%), m. p. and mixed m. p. 170·5—171·5°.

Similarly the acetic acid (XIII; B) (2·52 g.) gave the *ester iodide* (XXV; B) as yellow prisms (3·01 g.) (from methanol–ethyl acetate–ether), m. p. 168—170° (Found: C, 52·35; H, 6·1; N, 2·9%).

Also the quinolizine hydriodide (XXVI; B) (0·27 g.) was dehydrogenated with mercuric acetate in acetic acid to give the ester iodide (XXV; B) (0·20 g.), m. p. and mixed m. p. 168—170°.

2-*Ethoxycarbonylmethyl*-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-11b*H*-*benzo*[a]*quinolizine Hydriodide* (XXVI; A).—(i) The iodide ester (XXV; A) (0·97 g.) was hydrogenated in methanol (10 c.c.) with Adams catalyst (0·2 g.) at room temperature and atmospheric pressure. After filtration, concentration, and dilution with ether, the *hydriodide* separated as colourless needles (0·89 g., 91%), double m. p. 163—165° and 183·5—184·5° (Found: C, 51·5; H, 6·3; N, 3·0; I, 26·3. $C_{21}H_{31}O_4N,HI$ requires C, 51·5; H, 6·6; N, 2·9; I, 25·9%).

(ii) The iodide ester (XXV; A) (1·22 g.) was dissolved in methanol (40 c.c.) and saturated aqueous sodium hydrogen carbonate (40 c.c.) and treated at room temperature with sodium dithionite (4·0 g.) in two portions during 0·5 hr. The solution was left overnight, made strongly alkaline with 2N-sodium hydroxide, and extracted with ether. The hydriodide of the extracted base separated from ethanol as needles, m. p. 180—184° (1·02 g., 83%), identical with the previous preparation.

(iii) The iodide ester (1·2 g.) was treated in methanol (5 c.c.) with 2N-aqueous sodium carbonate. The anhydronium base was extracted with ether, dried (K_2CO_3), and recovered. To it was added 98% formic acid (0·17 g.) and the whole was kept at 60° for 2·25 hr., then

dissolved in 2N-hydrochloric acid. Potassium iodide was added. The hydriodide crystallised from methanol–ether as needles, m. p. and mixed m. p. 178—181° (1·0 g., 82%).

The isomeric iodide ester (XXV; B) (2·25 g.) was hydrogenated as described in (i) above. The *hydriodide* (2·17 g.) separated from methanol–ether as needles, m. p. 214·5—216·5° (Found: C, 51·8; H, 6·7; N, 2·9%).

A sample of the acid (m. p. 170—171°) corresponding to structure (XXVI) obtained from Drs. Brossi and Schnider [19] was esterified with ethanol and hydrogen chloride at room temperature; the ethyl ester was characterised as the hydriodide and crystallised from methanol–ether as needles, m. p. 214—216°. A mixed m. p. with the above sample showed no depression and infrared comparison of the two samples showed them to be identical (Found: C, 52·0; H, 6·6; N, 3·0%).

2-[N-(3,4-*Dimethoxyphenethyl*)*carbamoylmethyl*]-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-11bH-*benzo*[a]*quinolizine* (XXVII; A).—The ester hydriodide (XXVI; A) (2·44 g.) was hydrolysed with aqueous-alcoholic 10% potassium hydroxide (30 c.c.) at 95° for 2 hr. The alcohol was removed, the pH of the solution adjusted to pH 7, and the acid extracted with chloroform. The gummy acid was refluxed with 3,4-dimethoxyphenethylamine (1·8 g.), acetic acid (0·2 c.c.), and ammonium acetate (0·2 g.) in xylene (30 c.c.), in a Dean–Stark apparatus with separation of water, for 12 hr. The xylene was removed, water added, and the yellow solid filtered off and washed with water and ether. The *amide* separated from ethyl acetate as needles, m. p. 151·5—154·5° (1·58 g., 64%) (Found: C, 70·2; H, 8·1; N, 5·6. $C_{29}H_{40}O_5N_2$ requires C, 70·1; H, 8·1; N, 5·6%). The hydriodide had m. p. 227—228°. An amide of the same structure (XXVII; A) was later prepared by Brossi and Schnider [19] by a different route and had m. p. and mixed m. p. 152—154°; infrared comparison in Nujol showed them to be identical.

2-(3,4-*Dihydro*-6,7-*dimethoxy*-2-*isoquinolylmethyl*)-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-11bH-*benzo*[a]*quinolizine Dihydrobromide* (XXVIII, *A*) [(±)O-*Methylpsychotrine*].—The amide (XXVII; A) (2·42 g.) was heated in benzene (40 c.c.) with phosphorus oxychloride (6 c.c.) for 0·5 hr., whereupon a red oil separated. The solvent was removed and the residue dissolved in water and basified with 2N-sodium carbonate. The base was extracted with ether (3 times) and converted into the dihydrobromide which separated from methanol–ether as yellow nodules (2·25 g., 68%), m. p. 197—204°, softens at 195° [(+)-*O*-Methylpsychotrine dihydrobromide [27] has m. p. 190—200°] (Found, in air-dried specimen: C, 51·4; H, 6·25; N, 4·4. $C_{29}H_{38}O_4N_2$,2HBr,$2H_2O$ requires C, 51·5; H, 6·6; N, 4·1%). Drying at 100° did not remove the water of crystallisation and the same analysis was obtained.

(±)-*Emetine* (XXII; Aa_1) *and its Resolution*: *Stereoisomers* (XXII; Ab_1, Bc_1, Bd_1).—*1st Route. Reduction of stereoisomers of dehydroemetinium salts* (XXI). (i) (±)-Emetine (XXII; Aa_1). Dehydroemetinium iodide hydriodide (XXI; Aa) (1·46 g.) was converted into the chloride hydrochloride by shaking it with silver chloride in aqueous methanol, and the solution was filtered and evaporated to dryness. The residue was dissolved in methanol (20 c.c.) and hydrogenated with Adams catalyst (0·2 g.) at room temperature and atmospheric pressure. After rapid uptake of 1 mol. of hydrogen the solution was filtered and ether was added. The *dihydrochloride* (1·0 g.) of base (XXII; Aa_1) crystallised as prisms, m. p. 252—257° (sinters at 247°). A mixed m. p. with (+)-emetine dihydrochloride gave no depression. An infrared comparison in Nujol showed the two to be very similar but not identical (Found: C, 59·5; H, 7·9; N, 5·4; Cl, 12·4. $C_{29}H_{40}O_4N_2$,2HCl,$2H_2O$ requires C, 59·1; H, 7·9; N, 4·75; Cl, 12·0%. Found, in sample dried at 100°: C, 61·9; H, 7·7; N, 5·0. $C_{29}H_{40}O_4N_2$,2HCl,$0·5H_2O$ requires C, 61·9; H, 7·7; N, 5·0%). The dihydriodide, obtained by treatment of an aqueous solution of the dihydrochloride with sodium iodide, separated from methanol as woolly needles, m. p. 227—228°. A mixed m. p. with (+)-emetine dihydriodide (m. p. 228—229·5°; lit.,[28] m. p. 215—216°, 228—230°, 235—238°) showed no depression and a comparison of the two salts' infrared spectra showed no difference (Found in air-dried sample: C, 45·0; H, 5·6; N, 3·7; I, 32·5; H_2O, 4·3. $C_{29}H_{40}O_4N_2$,2HI,$2H_2O$ requires C, 45·1; H, 5·7; N, 3·6; I, 32·85; H_2O, 4·9. Found, in sample dried at 100°: C, 47·3; H, 5·2; N, 3·9; I, 34·5. $C_{29}H_{40}O_4N_2$,2HI requires C, 47·2; H, 5·7; N, 3·8; I, 34·5%). The base, derived from an aqueous solution of the hydrochloride by treatment with alkali, was a colourless amorphous solid, m. p. 68—70° (meniscus at 74°). A mixed m. p. with (−)-emetine (m. p. 74°) gave no

[27] Pyman, *J.*, 1917, **111**, 419.
[28] Karrer, *Ber.*, 1916, **49**, 2065; Keller, *Arch. Pharm.*, 1911, 521; Carr and Pyman, *J.*, 1914, **105**, 1604.

depression and the infrared spectra (in CS_2) of the two were identical. The (±)-base (XXII; Aa_1) (0·5 g.) in methanol was treated with (+)-dibenzoyltartaric acid (0·57 g., 2 mol.) in methanol–ethyl acetate: ethyl acetate was then added to turbidity and the solution seeded with the authentic salt. The (−)-*emetine bisdibenzoyltartrate* slowly crystallised and after two recrystallisations from methanol–ethyl acetate had m. p. 182—182·5° (decomp.), $[\alpha]_D^{20}$ −61·4° ±0·5° (*c* 1·002 in MeOH). An authentic specimen had m. p. 180—181°, $[\alpha]_D^{20}$ −62° (*c* 1·00 in MeOH); a mixed m. p. gave no depression and the infrared spectra were identical (Found: C, 64·6; H, 6·5; N, 2·7. $C_{29}H_{40}O_4N_2,C_{36}H_{28}O_{16},H_2O$ requires C, 64·9; H, 5·9; N, 2·3%). The (−)-base, obtained from this salt, with hydrochloric acid and sodium iodide gave the (+)-dihydriodide (sparingly soluble in water), needles (from methanol–ether), m. p. 228—230° (sinters at 225°), $[\alpha]_D^{19}$ +26·25° ±1·75° (*c* 0·571 in chloroform). An authentic sample had m. p. 228—229°, $[\alpha]_D^{19}$ +22·2° ±0·9° (in chloroform) (Found, in sample dried at 100°: C, 46·5; H, 5·8; I, 33·7. Calc. for $C_{29}H_{40}O_4N_2,2HI,H_2O$: C, 46·2; H, 5·9; I, 33·65%). In addition the (+)dihydrochloride was prepared from the (−)-dibenzoyltartrate in 82% yield, as needles (from methanol–ethyl acetate–ether), m. p. 235—250°, $[\alpha]_D^{20}$ +44·85° ±0·95° (*c* 1·07 in chloroform). An authentic specimen had m. p. 235—250°, $[\alpha]_D^{23}$ +46° (in chloroform) {lit.,[29] m. p. 235—250°, $[\alpha]_D^{20}$ +55° (in chloroform)} (Found: C, 57·0; H, 8·35; N, 4·4; H_2O, 8·0. Calc. for $C_{29}H_{40}O_4N_2,2HCl,3H_2O$: C, 57·3; H, 8·0; N, 4·6; H_2O, 8·9%). A mixed m. p. between these salts and authentic samples gave no depression and the infrared spectra (in KBr) of each pair were identical.

From the mother-liquor, after removal of a further small amount of the dihydriodide of base (XXII; Aa_1), the second isomer (cf. XXII; Aa_2) was obtained only as amorphous salts. The *dihydrochloride* had m. p. 235—240° (Found: C, 60·0; H, 7·5; N, 4·9; Cl, 12·6. $C_{29}H_{40}O_4N_2,2HCl,H_2O$ requires C, 60·95; H, 7·8; N, 4·9; Cl, 12·4%).

(ii) The dehydroemetinium iodide hydriodide (XXI; Ab) (1·80 g.) was converted into the chloride hydrochloride and reduced as described above. The *dihydrochloride* of base (XXII; Ab_2) crystallised readily as prisms (0·8 g.), m. p. 250—270°, softening at 240° (Found, in air-dried sample: C, 60·35; H, 8·3; N, 4·5. $C_{29}H_{40}O_4N_2,2HCl,H_2O$ requires C, 60·95; H, 7·8; N, 4·9%). This stereoisomer was examined by paper chromatography by the method described below and was found to be homogeneous and readily separated from emetine.

(iii) (*a*) The amorphous dehydroemetinium iodide hydriodide (XXI; Bc) (0·8 g.) in methanol (10 c.c.) was treated portionwise with sodium borohydride (1·0 g.) at 20°. After 0·5 hr. the solvent was removed and the residue treated with 2N-sodium carbonate and benzene. The benzene extracts were washed with water, then evaporated, and the product was converted into the *dihydrochloride* of base (XXII; Bc_1). This salt crystallised from methanol–ether as colourless prisms (0·28 g.), m. p. 261—267° (sinters at 258°). It can be separated readily from emetine by paper chromatography in the usual solvent system, and gave only one spot (Found, in air-dried sample: C, 59·3; H, 7·7; N, 4·8; Cl, 12·1. $C_{29}H_{40}O_4N_2,2HCl,2H_2O$ requires C, 59·1; H, 7·9; N, 4·75; Cl, 12·0%). The other epimer was not obtained. Comparison with an emetine isomer prepared by Drs. Brossi and Schnider [19] by m. p., mixed m. p., paper chromatography, toxicity, amœbicidal evaluation *in vivo*, and infrared spectroscopy showed them to be identical.

(*b*) The amorphous dehydroemetinium iodide hydriodide (XXI; Bc) (2·0 g.) was converted into the chloride hydrochloride in water and methanol with silver chloride (from 0·25 g. of silver nitrate) and hydrogenated in methanol (30 c.c.) with platinum oxide (0·18 g.). The solution was filtered, concentrated and diluted with ether and hydrochloric acid (0·1 c.c.). The dihydrochloride of base (XXII; Bc_1) separated as prisms (0·8 g.), m. p. 267—274° (decomp.), identical with the above specimen on paper chromatography.

(iv) Dehydroemetinium iodide hydriodide (XXI; Bd) (0·75 g.) was treated in methanol (15 c.c.) with potassium borohydride (0·3 g.) at 0°. The product was isolated after 1 hr. at 20° as the *dihydrochloride* of base (XXII; Bd), prisms (0·17 g.) (from methanol–ether), m. p. 215—220° (Found, in air-dried sample: C, 55·0; H, 7·8; N, 4·5; Cl, 11·9; loss on drying at 100°, 8·1. $C_{29}H_{40}O_4N_2,2HCl,4{\cdot}5H_2O$ requires C, 54·8; H, 8·1; N, 4·4; Cl, 11·1; $3H_2O$, 6·75. Found, in sample dried at 100°: C, 60·0; H, 7·6; N, 4·9. $C_{29}H_{40}O_4N_2,2HCl,1{\cdot}5H_2O$ requires C, 60·0; H, 7·8; N, 4·8%). Paper chromatography gave a single spot, easily separated from that of the salts of emetine and (XXII; Bc_1). This isomer (Bd_1) was also obtained by Drs. Brossi and Schnider [19] and m. p., mixed m. p., infrared spectroscopy, and paper chromatography showed them to be identical.

[29] Pyman, *J.*, 1914, **105**, 1591.

2nd Route. From stereoisomers of tetradehydroemetinium salts (XXIII). (i) *Salts of bases* (XXII; Ab_2 *and* Aa_1). Tetradehydroemetinium iodide hydriodide (XXIII; A_1) (2·07 g.) was shaken in hot water (75 c.c.) with silver chloride (from silver nitrate, 2 g.). The resulting chloride hydrochloride in methanol (20 c.c.) was reduced catalytically with platinum oxide (0·1 g.) at room temperature and pressure. After two mols. of hydrogen had been taken up the solution was filtered, concentrated, and diluted with ether. The *dihydrochloride* of base (XXII; Ab_2) separated as prisms (1·0 g., 60%), m. p. 245—260°, sinters 235°. Paper chromatography gave a single spot identical with that of isomer (Ab_2) obtained as described above. This identity was confirmed by the amœbicidal activity (Found: C, 60·43; H, 7·75; N, 4·6; Cl, 12·2. $C_{29}H_{40}O_4N_2,2HCl,H_2O$ requires C, 60·95; H, 7·8; N, 4·9; Cl, 12·4%). The mother-liquor yielded on concentration two small further crops of dihydrochlorides which were mixtures (XXII; Aa_1 and Ab_2). Unfortunately (Aa_1) was present in only very small amounts and could not be purified.

Sodium borohydride reduction in methanol gave isomer (Ab_2) in 50% yield.

(ii) *Salt of base* (XXII; Bc_1). The tetradehydroemetinium iodide hydriodide (XXIII; B) (0·5 g.) was converted into the chloride hydrochloride and hydrogenated in methanol (25 c.c.) with platinum oxide (0·1 g.). The dihydrochloride produced crystallised as prisms (0·15 g.), m. p. 255—265°, and had the same R_F value as (XXII; Bc_1) with which on this basis it was considered to be identical.

3rd Route. From (±)-O-*methylpsychotrine* (XXVIII; A). *Salts of bases* (XXII; Aa_1 *and* Ab_2). (±)-*O*-Methylpsychotrine dihydrobromide (XXVIII; A) (2·25 g.) was hydrogenated (1 mol.) in methanol (50 c.c.) with Adams catalyst (0·2 g.). The solution was then warmed and filtered. The alcohol was removed, water and 2N-sodium carbonate were added, and the base was extracted with ether and converted into mixed dihydrochlorides. Crystallisation from methanol–ether gave the dihydrochloride of base (XXII; Ab_2) as needles (0·88 g., 45%), m. p. 249—263° (Found, in sample dried at 100°: C, 62·1; H, 7·8; N, 5·0. $C_{29}H_{40}O_4N_2,2HCl,0{\cdot}5H_2O$ requires C, 61·9; H, 7·7; N, 5·0%). This isomer was identified as Ab_2 by its R_F value and mixed m. p. Concentration of the mother-liquor and addition of ether gave the dihydrochloride (0·84 g.), m. p. and mixed m. p. 247—257°, of base (XXII; Aa_1) (Found, in sample dried at 100°: C, 61·9; H, 7·65; N, 5·0%). Isomer (Aa_1) [(±)-emetine] was more difficult to free from traces of (Ab_2), as shown by paper chromatography, and three crystallisations were necessary to obtain a homogeneous sample, but the R_F of the final sample was the same as that of Aa_1 and emetine.

Paper Chromatography of Emetine Stereoisomers.—Ethyl methyl ketone (600 c.c.) was shaken with 2N-hydrochloric acid (200 c.c.). The ketone layer was used as the eluant in descending chromatography. Emetine dihydrochloride was used as a marker spot and given R_F 1 (distance travelled = 31 cm.). The R_F values are given in Table 1; in addition to the isomers (Ab_2, Bc_1, and Bd_1) in Table 1 which could be separated from emetine it was possible to separate isomers (Bc_1) and (Bd_1). The spots were detected with a reagent described by Brossi, Hafliger, and Schnider.[30]

(±)-*Rubremetinium Bromide* (XXIV).—Tetradehydroemetinium iodide hydriodide (XXIII; A) (0·37 g.) was oxidised in dilute acetic acid containing potassium acetate and mercuric acetate according to the procedure of Battersby, Openshaw, and Wood.[4] The bromide crystallised from dilute hydrobromic acid as orange-red needles (0·16 g.). When dried at 50° *in vacuo* for 1·5 hr. the salt had m. p. 177—185° with the meniscus at 197—205°, behaviour similar to natural (+)-rubremetinium bromide (Pyman [29] records m. p. 160—180°, meniscus at 195—205°) (Found, in air-dried specimen: C, 58·3; H, 6·2; N, 4·7. Calc. for $C_{29}H_{33}O_4N_2Br,2{\cdot}5H_2O$: C, 58·2; H, 6·4; N, 4·7%. Found, in sample dried at 100°: C, 62·2; H, 5·9; Br, 14·9. Calc. for $C_{29}H_{33}O_4N_2Br$: C, 62·9; H, 6·0; Br, 14·4%). The (±)-salt had $\lambda_{max.}$ (in H_2O) 257·5, 288, 300, 437·5 mμ (log ε 4·21, 4·22, 4·22, 4·44). (+)-Rubremetinium bromide had $\lambda_{max.}$ (in H_2O) 257·5, 288, 300, 437·5 mμ (log ε 4·21, 4·20, 4·21, 4·40). The infrared spectra (hexachloroethane KBr, Nujol) and the R_F (butanol, acetic acid, and water) were the same.

The authors are indebted to Dr. Schnitzer and his associates for the biological results, to Drs. Chopard and Wagland for the infrared spectra, to Drs. Cohen, Brossi, and Schnider for discussions, and to Mr. Tadd for experimental assistance.

Roche Products Limited,
Welwyn Garden City, Herts. [*Received, April 21st,* 1959.]

[30] Brossi, Hafliger, and Schnider, *Arzneimittel-Forsch.*, 1955, **5**, 62.

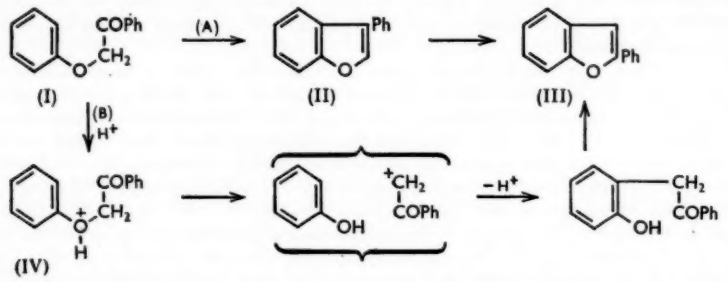
XUM

711. *Cyclodehydration Processes. Part II.* Migration of a Phenyl Group during Cyclisation of ω-Phenoxyacetophenone.*

By W. Davies and S. Middleton.

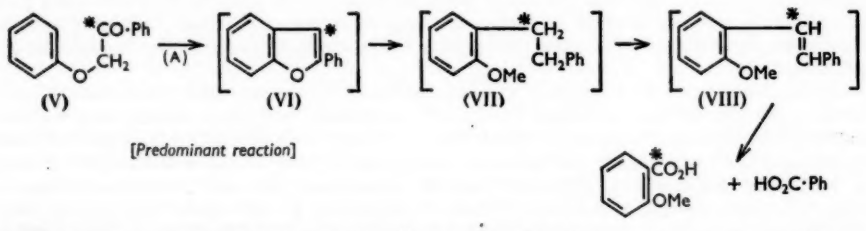
The use of a ^{14}C has shown that formation of 2-phenylbenzofuran during cyclisation of ω-phenoxyacetophenone with polyphosphoric acid at 132° is due to rearrangement of the normal cyclisation product, 3-phenylbenzofuran. The mechanism of this rearrangement is discussed.

In Part I * it was shown that cyclising ω-phenoxyacetophenone (I) by polyphosphoric acid at 80° for 3½ hr. gave an 82% yield of 3-phenylbenzofuran (II), but 132° for 2 hr. gave a 71% yield of 2-phenylbenzofuran (III); a mixture of the two was obtained at 110° in 2 hr. Further, since the 3- was rearranged to the 2-phenyl compound in 80% yield when heated with polyphosphoric acid at 132° for 2 hr., it was suggested that in condensations



the higher temperatures the latter was formed by rearrangement of the former (mechanism A). However, an alternative mechanism (B) involves fission between the oxygen atom and the CH_2 group [which could well occur if the oxonium salt (IV) was initially formed]. It was decided to distinguish between these mechanisms by use of [^{14}C].

ω-Phenoxy[*carbonyl*-^{14}C]acetophenone (V) was prepared from [1-^{14}C]acetyl bromide by standard procedures and treated with polyphosphoric acid at 132° for 3 hours, to give



predominantly compound (VI). This was reduced with sodium and ethanol to *o*-hydroxybibenzyl, which with methyl iodide gave the *o*-methoxy-compound (VII). Bromination with *N*-bromosuccinimide, followed by dehydrobromination with triethylamine, then gave *o*-methoxystilbene (VIII) which was oxidised with potassium permanganate to a mixture of benzoic and *o*-methoxybenzoic acid.

In this sequence mechanism A would give inactive benzoic and active *o*-methoxybenzoic acid, and mechanism B would give active benzoic and inactive *o*-methoxybenzoic acid.

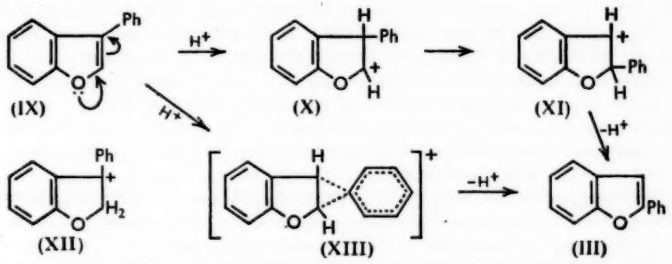
The mixed acids were treated with *p*-phenylazophenacyl bromide, and the azo-esters separated by chromatography. The benzoic ester contained only 0·3% of the combined

* Part I, *J.*, 1958, 822.

activities of both esters. Thus, under the conditions used, $\geqslant 0{\cdot}3\%$ of the 2-phenylbenzofuran can be formed by mechanism B or other mechanism not involving migration of the phenyl group.

The rearrangement of 3- to 2-phenylbenzofuran is apparently acid-catalysed since the 3-phenyl compound is not rearranged when heated alone; the reaction may be initiated by proton attack on the benzofuran nucleus. Since benzofuran undergoes electrophilic attack predominantly at the 2-position,[1] it would be expected that proton attack on 3-phenylbenzofuran would afford the carbonium ion (XII). This, however, would not be expected to rearrange, so reaction should not proceed further.

It is probable, however, that some proton-attack would take place at the 3-position (cf. IX). If the resulting carbonium ion had the classical structure (X), it could rearrange to the ion (XI) which could yield 2-phenylbenzofuran by loss of a proton. Alternatively,



Although the steps are represented as irreversible, this need not necessarily be so.

if the intermediate were the synartetic ion (XIII), it could rearrange to the 2-phenylbenzofuran by elimination of a proton. Rearrangements involving these types of intermediate are common; for example, carbonium ions similar to (X) and (XI) are involved in the formation of rearranged products during the deamination of 2-amino-1,1-diphenylpropan-1-ol,[2] and a bridged phenonium ion similar to (XIII) precedes formation of 1-phenylcyclohexene from *trans*-2-phenylcylohexanol.[3] The driving force for the rearrangement doubtless arises from the fact that isomer (III) is more conjugated than (II); that rearranged products have so far not been isolated during the cyclisation of compounds with an aliphatic side chain may be due to the absence of any marked difference between the degrees of conjugation of isomeric 2- and 3-alkylbenzofurans.

Experimental

ω-Phenoxy[carbonyl-^{14}C]*acetophenone* (V).—[1-^{14}C]Acetyl bromide (0·05 mc.), diluted with freshly distilled inactive material (5·0 ml.) was added dropwise during 10 min. to a stirred suspension of powdered aluminium bromide (23 g.) in dry benzene (20 ml.). The mixture was refluxed for 1 hr., cooled, decomposed with ice, and extracted with ether. The dried ($MgSO_4$) ether layer was evaporated on the steam-bath, the residue diluted with a " chaser " (15 ml. of α-bromonaphthalene), and the labelled acetophenone distilled at 90—91°/19 mm. (5·35 g., 67%). Bromination of an ether solution of this acetophenone by the method of Cowper and Davidson [4] gave [α-^{14}C]phenacyl bromide (82%) which with phenol (as described in Part I) gave ω-phenoxyacetophenone (V), m. p. 72·5—73° (73%).

Cyclisation.—The labelled compound was stirred with 10 parts of polyphosphoric acid (prepared as described in Part I) at 132° for 3 hr., after which the mixture was treated as described in Part I to give the labelled 2-phenylbenzofuran (VI), m. p. 120—121° (75%).

Labelled 2-Methoxystilbene (cf. VII).—2-Phenylbenzofuran (VI) was reduced with sodium

[1] Hartough and Meisel, " Compounds with Condensed Thiophene Rings," Interscience, New York, 1954.
[2] Benjamin, Schaeffer, and Collins, *J. Amer. Chem. Soc.*, 1957, **79**, 6160.
[3] Schaeffer and Collins, *ibid.*, 1956, **78**, 125.
[4] Cowper and Davidson, *Org. Synth.*, 1939, **19**, 24.

XUM

and ethanol by the method of Stoermer and Reuter [5] to *o*-hydroxybibenzyl, m. p. 83—84° (43%), which with methyl iodide (10 mol.) and potassium carbonate in boiling acetone gave the methoxy-compound (VII), b. p. 180—184°/18 mm. (93%).

o-Hydroxybibenzyl, like the *m*-hydroxy-compound,[6] could not be methylated by diazomethane.

Labelled 2-Methoxystilbene (VIII).—The bibenzyl derivative (0·81 g.) was refluxed with *N*-bromosuccinimide (0·68 g.) and benzoyl peroxide (10 mg.) in dry carbon tetrachloride (50 ml.) for 3 hr., cooled, and filtered to remove succinimide. Excess of triethylamine (2 ml.) was then added, and the mixture refluxed for 10 min., cooled, filtered to remove triethylamine hydrobromide, and evaporated. The residue was extracted with 1 : 1 benzene–light petroleum (b. p. 40—60°), and the extract chromatographed on silica with the same solvent mixture as developer. The fraction with blue fluorescence in ultraviolet light was collected and evaporated, to give the pale yellow stilbene derivative, m. p. 60—62° (0·68 g., 85%).

Oxidation. The stilbene (0·68 g.) was refluxed with potassium permanganate (4·5 g.) for 15 min. in acetone (50 ml., previously treated with permanganate) and water (30 ml.). The mixture was then diluted with water and acidified with concentrated hydrochloric acid, and solid sodium sulphite added to remove manganese dioxide. An ether extract of the resultant solution was extracted with sodium carbonate solution, which, after acidification with hydrochloric acid, yielded to methylene chloride the mixed acids as a pale brown solid.

During preliminary experiments with inactive material, it was found that neither *o*-hydroxy- nor *o*-methoxy-bibenzyl could be satisfactorily oxidised by chromic oxide–acetic acid, or acid, neutral or alkaline potassium permanganate.

p-*Phenylazophenacyl Bromide.*—*p*-Aminoacetophenone [7] (1 mol.) and nitrosobenzene (1 mol.) in glacial acetic acid overnight gave *p*-phenylazoacetophenone as orange-red plates (from ethanol), m. p. 114—115° (lit.,[8] m. p. 114·5—116°). Bromination in acetic acid [9] then gave the bromo-compound (54%) as red-orange prisms, m. p. 103—104° (lit., m. p. 104—105° [10], 92° [11], 103° [12], 104—105° [9]).

Separation of the Mixed Acids.—The mixed acids obtained by oxidation as above were dissolved in 10% sodium hydroxide solution (50 ml.), and the mixture made just acid to Cresol Red by addition of dilute sulphuric acid. A hot solution of *p*-phenylazophenacyl bromide (2·0 g.) in ethanol (150 ml.) was then added, the mixture refluxed for 1 hr. and cooled, and the resultant orange crystals were filtered off. After drying, these were chromatographed in benzene on silica, with benzene as developer.

Three distinct bands separated. The first, a narrow orange-red band, was readily eluted from the column; evaporation of the eluant gave an orange solid of indefinite m. p. which was rejected since it gave a positive Beilstein–Welch test for halogen and so presumably contained some unchanged *p*-phenylazophenacyl bromide. The second, orange band was broad and was also readily eluted by benzene. Evaporation of the eluant gave *p*-phenylazophenacyl benzoate, orange needles (from ethanol), m. p. and mixed m. p. 171—172° (Sugiyama *et al.*[12] report m. p. 169—169·5°).

The third, red-orange band was also broad but moved much more slowly. It was readily eluted, however, by benzene–ethyl acetate (10 : 1). Evaporation gave p-*phenylazophenacyl* o-*methoxybenzoate*, orange plates (from ethanol), m. p. and mixed m. p. 117—118° (Found: C, 70·5; H, 5·0; N, 7·7. $C_{22}H_{18}O_4N_2$ requires C, 70·6; H, 4·8; N, 7·5%).

Determination of Activities.—Infinitely thick samples of the separated azo-esters were counted under the same geometrical conditions with an end-window Geiger–Müller counter. Counting rates (per minute) and σ values were: background 10·2, 0·18; background + benzoic ester 12·4, 0·19; background + *o*-methoxybenzoic ester, 1056, 4·2. Thus, R = (activity of benzoic ester)/(total activity of both esters) = $(12{\cdot}4 - 10{\cdot}2)/[(12{\cdot}4 - 10{\cdot}2) + (1056 - 10{\cdot}2)]$ = 0·0021, and $\sigma_R = 0{\cdot}0025$. Thus, with a certainty of 0·99, $R = 0{\cdot}0021 \pm 0{\cdot}00075$, *i.e.*, the benzoic ester contains $> 0{\cdot}3\%$ of the total activity of both esters.

[5] Stoermer and Reuter, *Ber.*, 1903, **36**, 3982.
[6] Brunn, *Kgl. norske Videnskab. Selskab. Forhandl.* 1950, No. 4; *Chem. Abs.*, 1953, **11163**.
[7] Kunckell, *Ber.*, 1900, **33**, 2641.
[8] Angeli, *Atti R. Accad. Lincei*, 1915, **24**, 1187.
[9] Ikeda, Webb, and Kepner, *Analyt. Chem.*, 1954, **26**, 1228.
[10] Schmid and Leyman, *Helv. Chim. Acta*, 1950, **33**, 1494.
[11] Masuyama, *J. Chem. Soc. Japan, Pure Chem. Sect.*, 1950, **71**, 402.
[12] Sugiyama, Harada, Mita, and Ueno, *ibid.*, 1951, **72**, 152.

The authors thank Imperial Chemical Industries of Australia and New Zealand for the award of a Research Fellowship (to S. M.), Dr. J. F. Duncan for advice on radiochemical techniques, and Drs. R. D. Brown and K. H. Pausacker for helpful discussions. Microanalyses were carried out by Dr. K. W. Zimmermann and his staff.

CHEMISTRY DEPARTMENT, UNIVERSITY OF MELBOURNE,
CARLTON, N.3, AUSTRALIA. [*Received, April 27th*, 1959.]

---

712. *Phospholipids. Part V.* The Hydrolysis of the Glycerol 1-Esters of Myoinositol 1- and 2-Phosphate.*

By D. M. BROWN, G. E. HALL, and R. LETTERS.

Myoinisitol 2-phosphate and myoinositol 1-phosphate (isolated after acid rearrangement of the former) each give a glycerol diester on treatment with glycidol. The esters are readily hydrolysed by base, each giving a mixture of inositol 1(and 2)-phosphate and glycerol 1(and 2)-phosphate. The ratios of inositol 1- to 2-phosphate and of glycerol 1- to 2-phosphate are the same for each ester, showing that the corresponding cyclic 1,2-phosphates are intermediates. The ratio of total inositol phosphate to glycerol phosphate, however, differs and serves to distinguish the two esters.

When the glycerol esters are treated with periodate (1 mol.) followed by phenylhydrazine, each is converted, without significant phosphate migration, into its parent inositol phosphate. Two methods are therefore available for establishing the position of linkage of the inositol residue in the natural phosphoinositides.

THERE is good evidence that many of the simpler naturally occurring phosphoinositides are myoinositol esters of diacyl-L-α-glycerol phosphates.[1,2,3] In these, the major structural problem relates to the position of the phosphate–inositol linkage. There are, in theory, six possible isomers, which include two pairs of optical isomerides. The problem has been rendered difficult by the availability of only one myoinositol phosphate, *viz.*, the 2-isomer (II), as reference compound.[4] The structural problem is further complicated by the fact, not generally recognised until recently, that the inositol phosphate formed on hydrolysis of the lipid must almost certainly consist of a mixture of two or more isomers. If the hydroxyl groups on the inositol residue of a lipid did not take part in this hydrolysis, then glycerol 1- and 2-phosphate alone would be produced (cf., *inter alia*, the hydrolysis under similar conditions of phosphatidyl-choline and -ethanolamine[5]). But inositol phosphate is in general a hydrolytic product, which means that the inositol hydroxyl groups are involved and that therefore an inositol cyclic phosphate is an intermediate. Consequently the inositol phosphate formed must be assumed to be an isomeric mixture.

Our earlier experiments,[6,7] indeed, showed that a vicinal hydroxyl group in a six-membered ring, as in (I; R = $Ph{\cdot}CH_2$ or Me) was effective in the base-catalysed trans-esterification leading to the cyclic phosphate with expulsion of the R group. The hydrolysis of the *cis*- and the *trans*-compound (I; R = glycerol-1) gave both 2-hydroxycyclohexyl phosphate and glycerol phosphate, the former predominating from the *cis*-isomer, the latter from the *trans*-isomer. The kinetics of the hydrolyses showed that the factors which decided the relative importance of the two pathways were multiple, and it

* Part IV, *J.*, 1959, 357.

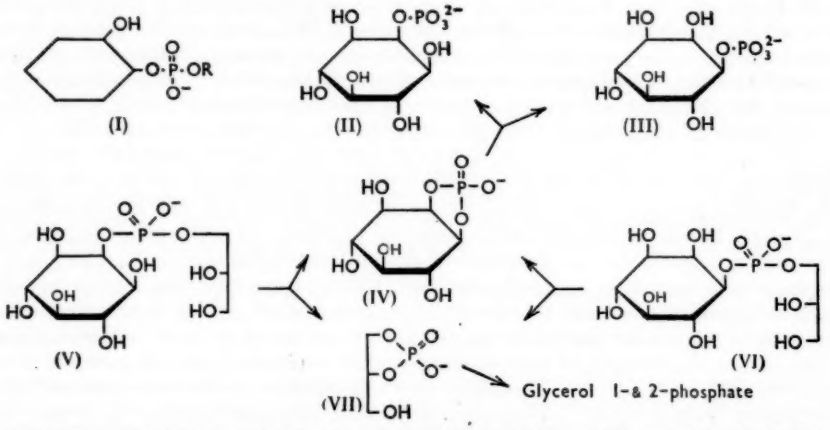
[1] Hanahan and Olley, *J. Biol. Chem.*, 1958, **231**, 813.
[2] Morelec-Coulon and Faure, *Bull. Soc. Chim. biol.*, 1958, **40**, 1307.
[3] Folch and LeBaron, *Canad. J. Biochem. Physiol.*, 1956, **34**, 305.
[4] Brown and Hall, *J.*, 1959, 357.
[5] Baer and Kates, *J. Biol. Chem.*, 1948, **175**, 79; 1950, **185**, 615.
[6] Brown and Higson, *J.*, 1957, 2034.
[7] Brown, Hall, and Higson, *J.*, 1958, 1360.

XUM

was concluded that the stereochemical considerations *per se* could not be applied directly to the structural elucidation of phosphoinositides based only on product ratios.

The present experiments with the glycerol esters of myoinositol 1- and 2-phosphate, *i.e.*, (VI) and (V) respectively, show that hydrolytic evidence can be used to demonstrate, in the instances studied, the position of esterification on the inositol residue. Another method giving the same results is also described, which may be of general applicability and avoids phosphoryl migration. Since completion of the work Pizer and Ballou [8] have shown convincingly that the phosphoinositide derived from soya bean is the diacyl glycerol ester of myoinositol 1-phosphate (III) since alkaline hydrolysis yielded inositol 2-phosphate and an *optically active* inositol 1-phosphate; the intermediate cyclic 1,2-phosphate must therefore have been active, a situation which could not have arisen if the original position of esterification in the inositide had been the 2-hydroxyl group.

When the work was begun, myoinositol 2-phosphate was the only available starting material from which to prepare a glycerol ester, but another isomer was required for comparative degradation studies. Dr. C. E. Ballou informed us that acid-isomerisation of the 2-phosphate led to its mixture with the 1-phosphate (III) and that the latter could be isolated. The cyclohexylammonium salt has since been described.[8,9] but we include a simple preparation of this salt, suitable for its isolation in quantity. This salt differs from that of the 2-phosphate in infrared spectrum, degree of hydration, and paper-chromatographic behaviour. Moreover, when inositol 2-phosphate was treated with dicyclohexylcarbodi-imide in dimethylformamide it gave inositol 1,2-phosphate (IV) isolated in high yield as the crystalline ammonium salt. Posternak [10] and Pizer and Ballou [8] have recently described the corresponding barium and cyclohexylamine salts respectively, and, like these authors, we find that the cyclic phosphate is rapidly hydrolysed by base to inositol 1- and 2-phosphate.



Inositol 2-phosphate reacted under carefully controlled conditions with glycidol, best in aqueous solution at pH 5·4, to give the glycerol 1-ester (V). The product was relatively unstable but could be purified by ion-exchange chromatography and isolated as a barium salt. By similar means inositol 1-phosphate afforded the glycerol ester (VI). Experiments recorded below show that esterification had not been accompanied by appreciable phosphoryl migration and that little, if any, of the glycerol 2-esters had been formed.

When the ester (V) was treated with N-sodium hydroxide at 60°, hydrolysis was complete in 30 minutes and chromatography then showed that glycerol phosphate and

[8] Pizer and Ballou, *J. Amer. Chem. Soc.*, 1959, **81**, 915.
[9] Posternak, *Helv. Chim. Acta*, 1959, **42**, 390.
[10] *Idem, ibid.*, 1958, **41**, 1891.

inositol phosphate were formed in addition to glycerol and inositol, but that orthophosphate was absent. The phosphorylated products were resolved into glycerol 1- and 2-phosphate and inositol 1- and 2-phosphate. The same products were formed from ester (VI) on hydrolysis. The proportions of the phosphorylated products were next examined and because a relatively high degree of accuracy was required two methods of estimation were used. In the first the products were separated on chromatograms, the spots excised, and the phosphorus contents of the eluates determined. In the second method [11,12] the paper chromatograms were bombarded with neutrons, then cut into transverse strips, and the ^{32}P activities were measured. Summation of the activities under each peak allowed the proportions of the phosphorus-containing compounds to be calculated. The results (see Table 1) obtained by the two methods differ by at most $\pm 1\%$. Although there is very close agreement we feel, from our experience, that for this particular application the neutron activation method is the less accurate, but on the other hand when phosphate esters are poorly resolved on chromatograms they can be clearly distinguished by the activation technique.

Earlier work had shown that when glycerol 1,2-phosphate was hydrolysed by alkali the ratio of glycerol 1- to 2-phosphate produced was 45 : 55.[7,13] The cyclic inositol 1,2-phosphate, under the same conditions, gave the 1- and the 2-isomer in a ratio of 69 : 31. It is evident from Table 1 that these product ratios are identical with those obtained in

TABLE 1. *Alkaline hydrolysis of inositol glycerol phosphates.*

	Ratios of phosphate esters					
	Inositol 1- : inositol 2-P		Glycerol 1- : glycerol 2-P		Glycerol-P : inositol-P	
Myoinositol ester	*a*	*b*	*a*	*b*	*a*	*b*
2-(Glycerol 1-phosphate) (V)	69 : 31	70 : 30	44 : 56	45 : 55	61 : 39	60 : 40
1-(Glycerol 1-phosphate) (VI)	70 : 30	70 : 30	44 : 56	45 : 55	65 : 35	66 : 34

[a] Estimated by radioactivation analysis. [b] Estimated chemically after elution from paper chromatograms.

the hydrolyses of the glycerol esters (V) and (VI). This is clear evidence that the cyclic phosphates (IV) and (VII) are obligatory intermediates in the two competing hydrolytic pathways. It also shows, in agreement with the conclusions of Pizer and Ballou,[8] that in the hydrolysis of the 1-isomer (V) little or no attack by the *trans*-6-hydroxyl group in the inositol residue had occurred, consistently with the lack of evidence for the production of a third isomeric inositol phosphate. The esters (V) and (VI), therefore, show the expected close correspondence in their hydrolytic behaviour to the glycerol ester of *cis*-2-hydroxycyclohexyl phosphate; [7] in particular, the high rate of hydrolysis is noted, characteristic of dialkyl phosphates carrying two vicinal hydroxyl groups, but the evidence suggests that there is greater conformational rigidity in the inositol compounds since in these a *trans*-hydroxyl group does not compete effectively whereas it does in the cyclohexane-1,2-diol series. Table 1 shows that the ratio of total glycerol phosphate to total inositol phosphate in the hydrolysate from (V) is not the same as that from (VI). Thus the two esters can be distinguished by this criterion. This is not unexpected since if we consider the pathway by which inositol 1,2-phosphate is formed with expulsion of the glycerol residue, the transition state in the internal displacement [14] cannot be the same for each ester. The present evidence, therefore, strongly suggests that the position of linkage of the inositol residue in phosphoinositides based on (V) or (VI) could be established by a determination of the ratio of alkaline hydrolysis products. One proviso must, however, be made. Compound (V) is a (±)-glycerol ester, but (VI) as here prepared is presumably a mixture of the

[11] Winteringham, Bridges, and Hellyor, *Biochem. J.*, 1955, **59**, 13.
[12] Maruo and Benson, *J. Amer. Chem. Soc.*, 1957, **79**, 4564.
[13] Ukita, Nagasawa and Irie, *Pharm. Bull.* (*Japan*), 1957, **5**, 127.
[14] Brown, Magrath, Neilson, and Todd, *Nature*, 1956, **177**, 1124.

XUM

(±)-glycerol esters of (±)-inositol 1-phosphate and it is conceivable that the diastereoisomerides in (VI) could give different proportions of products on hydrolysis, the observed value being the mean of these. Further study of this point is needed. The evidence further indicates that inositides based on esters (V) and (VI) could be distinguished from those based on inositol 4- or 5-phosphate (cf. ref. 8) since the latter should give a high ratio of glycerol phosphate to inositol phosphate owing to poor or ineffective competition of the *trans*-vicinal hydroxyl groups.

The value of a degradative method which would proceed with little or no phosphoryl migration is obvious. It is well known that the rate of oxidation of myoinositol by periodate is considerably less than that of glycerol. We found that glycerol 1-phosphate was almost completely oxidised by periodate (1 mol.) in 10—15 minutes whereas less than 5% of inositol 2-phosphate was degraded in the same time. It has been shown, too, that the periodate oxidation product from glycerol phosphate, glycollaldehyde phosphate, is largely broken down to orthophosphate when treated mildly at pH 6 with phenylhydrazine (1 mol.).[15] The glycerol esters (V) and (VI) were each treated with periodate, followed by phenylhydrazine, and the products were chromatographed.

Myoinositol 1-(glycerol 1-phosphate) (VI) yielded orthophosphate and inositol 1-phosphate, no evidence for any of the 2-isomer being found. The ester (V) gave largely inositol 2-phosphate together with small amounts of orthophosphate and inositol 1-phosphate. The product ratios, determined as before, are given in Table 2. They show that specific degradation of the esters can be effected with little or no phosphoryl migration, presumably through the glycollaldehyde ester (inset). The experiments, too, confirm the structures (V) and (VI); since the glycerol residue was oxidised it was evidently esterified at the 1-position and, in addition, the inositol phosphate recovered from the degradation was in each case that used in the preparation of the corresponding diester. When inositol phosphate is oxidised with more than one mol. of periodate much inorganic phosphate is formed, apparently through over-oxidation of the ultimate cleavage product $H_2PO_3{\cdot}O{\cdot}CH(CHO)_2$.[16] This could account for the small amount of inorganic phosphate produced from (V) and a larger amount from (VI) which has a *cis*-diol grouping.

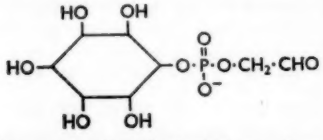


TABLE 2. *Periodate degradation of inositol glycerol phosphates.*

	Phosphates produced (%)					
	Inositol 1-P		Inositol 2-P		ortho-P	
Myoinositol ester	*a*	*b*	*a*	*b*	*a*	*b*
2-(Glycerol 1-phosphate) (V)	5	5	86·5	85	8·5	10
1-(Glycerol 1-phosphate) (VI)	68	67	—	—	32	33

[a] [b] See Table 1.

Methods are now available for converting phosphatidylinositols into the corresponding inositol glycerol phosphates,[2,17,18] so that the value of the procedures described above can now be tested. Their application to the phosphoinositide from horse liver will be reported later.

EXPERIMENTAL

Biscyclohexylammonium Myoinositol 1-Phosphate (with Mr. B. F. C. CLARK).—Myoinositol 2-phosphate (1·0 g.) was boiled under reflux in 80% acetic acid (90 ml.) for 50 min., and the solvent then removed *in vacuo*. The residue was evaporated several times with ethanol to remove remaining acetic acid. It was dissolved in water (7 ml.), cyclohexylamine (1·1 ml.)

[15] Fleury, Courtois, and Desjobert, *Bull. Soc. chim. France*, 1952, **19**, 458.
[16] Courtois and Ramet, *Bull. Soc. Chim. biol.*, 1945, **27**, 610.
[17] Dawson, *Biochim. Biophys. Acta*, 1954, **14**, 374.
[18] Hawthorne and Hübscher, *Biochem. J.*, 1959, **71**, 195.

was added, and the solution was extracted with ether (3 × 7 ml.) to remove excess of cyclohexylamine. After evaporation of the aqueous phase, the residue was dissolved in warm 92% methanol (10 ml.), and the solution filtered. Ether was added to near turbidity, and the solution set aside at room temperature for 12 hr. The crystalline product was collected and dissolved in warm methanol–water (10 : 0·5 ml.), and ether (~12 ml.) was added. After 8 hr. at 0° the product (320 mg.) was collected, washed with methanol–ether, and dried. It had m. p. 184—190° (decomp.) and was distinguished from the salt of the 2-phosphate by infrared spectroscopy and paper chromatography (Found, in material dried at 60° for 7 hr./0·1 mm. over P_2O_5: C, 46·0; H, 8·6; N, 6·0; P, 6·7. Calc. for $C_{18}H_{39}O_9N_2P,0·5H_2O$: C, 46·25; H, 8·6; N, 6·0; P, 6·6%).

Ammonium Myoinositol 1,2-*Phosphate* (with Mr. R. Nowack).—Myoinositol 2-phosphate (0·5 g.) was suspended in dry dimethylformamide (30 ml.) in which it was partly soluble. Dicyclohexylcarbodi-imide (0·45 g.) in dimethylformamide (3 ml.) was added and the mixture shaken. After 2 days the solution was filtered from dicyclohexylurea, and the filtrate was treated with concentrated ammonia solution to pH 10. The *ammonium salt* (0·33 g., 66%) which separated was collected by centrifugation, and washed with dry ethanol. It was very hygroscopic and was chromatographically homogeneous (Found, in material dried at 50°/0·1 mm. over P_2O_5: C, 28·0; H, 6·0; N, 5·35. $C_6H_{14}O_8NP$ requires C, 27·8; H, 5·4; N, 5·4%).

On hydrolysis with N-sodium hydroxide at 60° for 30 min. it gave inositol 1- and 2-phosphate, in a ratio of 69 : 31 as estimated by phosphorus analysis or by radioactivation analysis on the chromatographically separated phosphates.

Barium Myoinositol 2-(*Glycerol* 1-*Phosphate*).—A solution of myoinositol 2-phosphate [4] (198 mg.) and glycidol (0·3 ml.) in 0·08N-potassium hydroxide (11 ml., 1·15 equiv.) was boiled for 7 hr. Paper chromatography showed that the major product was inositol glycerol phosphate (together with small amounts of orthophosphate, glycerol phosphate, and inositol). The solution was diluted to 150 ml., adjusted to pH 8 with dilute ammonia solution, and percolated (0·5 ml./min.) through a column (15 × 15 cm.) of Dowex 2 × 8 resin (200—400 mesh; formate form). The effluent was re-percolated through the same column so that all but 12% of the total phosphate was absorbed. The column was washed with water (2 × 25 ml.), then 0·1N-formic acid (250 ml.) was percolated through the column, removing only the desired product. The formic acid eluant was freeze-dried, and the residue dissolved in water (20 ml.), and the solution was neutralised with barium hydroxide and concentrated to small volume. The barium salt was precipitated by addition of ethanol (15 vol.) and, after being set aside overnight at 0°, was collected by centrifugation, washed with ethanol (3 × 10 ml.), and dried (yield, (145 mg., 48%). Several more precipitations from water by ethanol then gave the pure *barium salt*, an amorphous, hygroscopic solid, which was chromatographically pure (Found, in material dried at 40°/6 hr. *in vacuo* over P_2O_5: C, 26·1; H, 5·0; P, 7·6. $C_{18}H_{36}O_{22}P_2Ba,2H_2O$ requires C, 25·8; H, 4·8; P, 7·4%).

Barium Myoinositol 1-(*Glycerol* 1-*Phosphate*).—Myoinositol 1-phosphate was obtained from the cyclohexylamine salt (350 mg.) by treatment with Dowex-50 resin. By the same procedure as above it was converted into the hygroscopic *barium myoinositol* 1-(*glycerol* 1-*phosphate*) (87 mg.) (Found, in material dried at 40° for 6 hr. *in vacuo*: C, 26·7; H, 5·1; P, 7·24. $C_{18}H_{36}O_{22}P_2Ba,H_2O$ requires C, 26·3; H, 4·6; P, 7·6%).

Paper Chromatography.—Whatman No. 1 paper (washed with 2N-acetic acid) was used, with the solvent system propan-2-ol–water–ammonia (*d* 0·880) (7 : 2 : 1 v/v) with descending-front chromatography (2 days). All the phosphorus-containing substances were adequately resolved. The R_P values quoted here are taken relative to inositol 2-(glycerol 1-phosphate) (V) as 1·0; inositol 1-(glycerol 1-phosphate) (VI) 0·91, glycerol 1-phosphate 0·65, glycerol 2-phosphate 0·75, inositol 1-phosphate 0·36, inositol 2-phosphate 0·43, orthophosphate 0·33, and inositol 0·9.

Phosphate esters were detected by the molybdate spray,[19] 1,2-glycols by the periodate–Schiff reagent,[20] and glycerol and inositol by the silver nitrate–alkali method.[21]

Hydrolysis of Inositol Glycerol Phosphates.—The phosphate esters (*ca.* 30 mg.) were hydrolysed in N-sodium hydroxide (0·5 ml.) at 60° for 30 min., and after removal of cations by addition of Dowex-50 (H^+ form) resin the solutions were run on chromatograms (see below). Inositol 1- and 2-phosphate and glycerol 1- and 2-phosphate were identified as the hydrolysis products,

[19] Hanes and Isherwood, *Nature*, 1949, **164**, 1107.
[20] Baddiley, Buchanan, Handschumaker, and Prescott, *J.*, 1956, 2818.
[21] Anet and Reynolds, *Nature*, 1954, **174**, 930.

XUM

in addition to inositol and glycerol. The ratios of phosphorylated products were obtained by phosphorus determinations [22] on eluates of excised spots or by radioactivation analysis after neutron activation of the paper chromatogram and are recorded in Table 1.

Radioactivation Analysis.—Chromatograms of the above hydrolysates were run on paper strips 4·5 cm. wide. The strips, after drying, were neutron-activated (pile factor 1) for two days and after a further two days were cut into 1 cm. transverse strips, and the activity in each was counted. The strips were further subdivided when peaks were incompletely resolved. The counts under each peak were summed, after corrections for the resolution of the counter-system and for background; the ratios are recorded in Table 1. The counting was repeated 3—4 times at intervals of about 2 days to ensure the constancy of the ratios and to check the half-life of the β-emitter. In all cases this corresponded to that of ^{32}P.

Periodate Degradation of Inositol Glycerol Phosphates.—Barium myoinositol 2-(glycerol 1-phosphate) (50 mg.) was dissolved in water (1·5 ml.), and sodium metaperiodate (40 mg.) added. The solution was centrifuged to remove precipitated barium metaperiodate, and the supernatant solution was adjusted to pH 6 with dilute formic acid. After 1 hr. a solution of phenylhydrazine (14 mg.), neutralised to pH 6 with formic acid, was added and the mixture left at 37° for 6 hr. Cations were removed by addition of Dowex-50 resin (H^+ form), and the solution was analysed on a chromatogram in the usual way. The phosphorylated products were identified by comparison with standards and were estimated by phosphate analysis on eluates and by neutron-activation. The results, together with those obtained with myo-inositol 1-(glycerol 1-phosphate) are recorded in Table 2. Traces of starting material were sometimes observed on chromatograms of the reaction mixtures, but were ignored in the calculation of the product ratios.

We thank Dr. A. G. Maddock and his colleagues for valuable advice, and Sir Alexander Todd, F.R.S., for his encouragement, and acknowledge with thanks a D.S.I.R. award (to G. E. H.) and an Earl Grey Memorial Fellowship (to R. L.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, May 4th,* 1959.]

[22] Allen, *Biochem. J.*, 1940, **34**, 858.

---

713. *The Stretching Frequencies of Metal–Oxygen Double Bonds.*

By C. G. BARRACLOUGH, J. LEWIS, and R. S. NYHOLM.

The infrared spectra of a number of compounds containing metal–oxygen double bonds have been measured. It is concluded that the presence of a metal=O bond can be correlated with a stretching frequency in the range 900—1100 cm.$^{-1}$. The potential diagnostic value of this band in inorganic chemistry is discussed, with particular reference to metal–oxygen systems wherein more than one type of bonding occurs.

THE rapid, and even occasionally the positive, detection of a metal–oxygen double bond in metal complexes is difficult. If we exclude those cases where the oxygen atom is also attached to a lighter atom (*e.g.*, M–O–H or M–O–C$\lesssim$ as in metal alkoxides which can be identified through O–H or O–C stretching frequencies), the two main kinds of metal–oxygen bond in metal complexes are (1) M=O and (2) M–O–M.

One of the major problems in a study of these systems is the difficulty of obtaining model compounds in which the presence of an M=O bond has been unambiguously established by structural investigations (*e.g.*, *X*-ray or electron diffraction). Unfortunately, many compounds which are normally written as monomers with an M=O link are polymers with a chain structure, *i.e.*, M–O–M–O–M–. For instance, $TiOSO_4$ has recently been found to be polymeric [1] with such a chain structure.

A number of compounds have been studied whose spectra contain the M=O stretching frequency, to ascertain how it varies in different circumstances. The compounds are conveniently divided into three groups (Table 1). Class A contains those compounds in

[1] Lundgren, *Arkiv Kemi*, 1957, **10**, 397.

which there is only one metal–oxygen bond per metal atom, this bond having a high double-bond character. Class B is similar except that there are two such M=O bonds per metal atom. Class C contains all compounds with more than two M–O bonds, including complex oxides in which there may be a noteworthy decrease in double-bond character.

In Class A we have included those compounds containing one oxygen atom per metal atom and which *probably* contain metal–oxygen bonds with a high degree of double-bond character. Of these titanyl bisacetylacetone is a non-electrolyte in nitrobenzene and is monomeric in benzene;[2] hence it is one of the few compounds in which the titanyl group (Ti=O) may be considered to be present. Comparison of the spectrum of this compound with that of trisacetylacetonetitanium(III), shows the presence of a new band at 1087 cm.$^{-1}$ which is strong and sharp, and this is considered to be the Ti=O stretching frequency. In the majority of titanyl complexes one or more very broad absorption bands are normally observed in the 800—900 cm.$^{-1}$ region, which may be associated with the lower bond order and high degree of degeneracy of the vibrations to be expected in a system of the type (–Ti–O–Ti–O–Ti–O–). Thus $TiOSO_4$ shows very broad bands at 820 and 920 cm.$^{-1}$, and potassium titanyl oxalate, generally written as $K_2TiO(C_2O_4)_2$, has broad bands at 800 and 900 cm.$^{-1}$.

A closely related compound to the titanium complex is vanadyl bisacetylacetone which has recently been shown by *X*-ray diffraction to be a monomer [3] with a tetragonal-pyramidal arrangement of the five bonds about the metal atom. The absorption band at 995 cm.$^{-1}$ is taken as corresponding to the (V=O) stretching frequency. Vanadyl chloride has a monomeric molecule with a tetrahedral structure and shows a strong, sharp band at 1035 cm.$^{-1}$ which corresponds to the metal–oxygen stretching vibration.[4] For the other compounds listed in Class A the structures have not been unambiguously established. However, their formulation as monomeric molecules would involve a similar type of bonding, and in the cases of the vanadyl bisoxalate and potassium pentachloro-oxychromate and pentachloro-oxymolybdate complexes a sharp band is observed in a similar region of the spectrum. The magnetic moments of the last two compounds [$\mu_{eff.}$ = 1·82 B.M. for $(NH_4)_2CrOCl_5$; $\mu_{eff.}$ = 1·73 B.M. for K_2MoOCl_5] agree with their formulation as monomers. For vanadyl sulphate and the bismalonatovanadyl complex only one band would be expected on the basis of a simple structure, and the splitting of the bands may arise from a solid-state effect or alternatively the complexes may be polymeric. In the case of vanadyl sulphate pentahydrate the *X*-ray structure [5] has established an octahedral arrangement of five water molecules and one oxygen atom around each vanadium atom. The compound examined in Table 1, however, was the anhydrous form as it was not found possible to obtain a satisfactory spectrum of the hydrated species. The vanadyl bisoxalate and bismalonate complexes have been formulated as dimers involving two bridging oxygen groups [6] but no direct evidence for this formulation has been obtained.

It has been suggested [7] that the V=O stretching frequency in some vanadyl chelates of tetraphenylporphin derivatives occurs at 1337 cm.$^{-1}$, but this gives a force constant of approximately 12 millidynes/Å, as mentioned by Ueno and Martell.[7] This is well outside the ranges given in Table 2.

For the molecules containing two oxygen atoms per metal atom in Class B an electron-diffraction study of chromyl chloride shows the molecule to be tetrahedral and it is reasonable to assign a similar structure to CrO_2F_2. The spectra show two strong bands in the 1000 cm.$^{-1}$ region and these have been assigned to the two metal–oxygen stretching modes expected for molecules of this type.[8]

[2] Cox, unpublished work.
[3] Dodge, *Univ. California Rad. Lab. Publ.*, 8225.
[4] Miller and Cousins, *J. Chem. Phys.*, 1957, **26**, 329.
[5] Lundgren, *Rec. Trav. chim.*, 1956, **75**, 585.
[6] Palmer, " Experimental Inorganic Chemistry," Cambridge Univ. Press, 1954, p. 320.
[7] Ueno and Martell, *J. Phys. Chem.*, 1956, **60**, 934.
[8] Hobbs, *J. Chem. Phys.*, 1958, **28**, 1220.

XUM

The three oxides listed in Class C are of special interest and will be considered in more detail. Vanadium pentoxide is polymeric but the *X*-ray data [9] show that the structure may be regarded as distorted VO_5 trigonal-bipyramids sharing four corners and leaving one oxygen atom bonded effectively only to one vanadium atom. It seems reasonable to interpret the spectrum by considering the sharp band at 1020 cm.$^{-1}$ as representing stretching vibrations of the independent V=O groups, while the broader and weaker band at 825 cm.$^{-1}$ represents vibrations of the vanadium–oxygen layer lattice. The V–O distance of the isolated oxygen atom is 1·54 Å, similar to that in $VOCl_3$ (V–O = 1·56 Å [10]) and also to that in vanadyl bisacetylacetone (V–O = 1·59 Å [3]).

Chromium trioxide is described [11] as distorted CrO_4 tetrahedra sharing two corners to form chains, with only weak van der Waals forces operating between the chains. The band at 969 cm.$^{-1}$ in the spectrum is considered to represent the stretching frequency of the two free Cr–O groups, while the much broader band at 893 cm.$^{-1}$ represents vibrations of the continuous chromium–oxygen chain. The structure of molybdenum trioxide has been given by Anderson and Magnelli.[12] It may be regarded as containing distorted MoO_6 octahedra in which three of the oxygen atoms are common to three MoO_6 octahedra, two of the oxygen atoms are common to two octahedra, and the sixth oxygen atom is unshared, *i.e.*, bound to only one molybdenum atom. As in the previous two cases the strong band at 985 cm.$^{-1}$ is regarded as being due to stretching vibrations of the independent Mo–O groups while the two much broader bands at longer wavelengths are attributed to the two different (Mo–O–Mo) continuous structures.

The data in Table 1 show that most of the metal–oxygen stretching frequencies fall within the range 900—1100 cm.$^{-1}$. However even for a particular metal the frequencies can vary widely as the bond order changes. For example, Jones [13] quotes the uranyl group as giving asymmetric stretching frequencies between 850 and 1000 cm.$^{-1}$ depending upon the nature of the compound. It is of interest to consider the information which is available on stretching force constants and these results are quoted in Table 2.

TABLE 1. *Metal–oxygen stretching frequencies.*

Compound *	State	Frequency (cm.$^{-1}$) †	Compound *	State	Frequency (cm.$^{-1}$) †
	Class A			Class C	
$TiO(acac)_2$	Nujol mull	1087	V_2O_5	Nujol mull	825 m, b, 1020 s
$VOSO_4$	,,	987, 1003, 1020	CrO_3	,,	893 m, b, 969 s
VO(acac)	,,	995 s, sh	MoO_3	,,	813 m, b, 870 s, br, 985 s
$(NH_4)_2[VO(ox)_2,2H_2O]$	,,	976 s, sh	$KMnO_4$	,,	900 s, br
$(NH_4)_2[VO(mal)_2,4H_2O]$	,,	967, 977	$KReO_4$	,,	913 s, br
K_2MoOCl_5	,,	967	K_2CrO_4	Soln. in formamide	880 s, br
K_2CrOCl_5	Soln. in formamide	952	K_2CrO_3Cl	,,	906 w, 951 s
$VOCl_3$	Liquid	1035 [a] s, sh	$K_2Cr_2O_7$	,,	906 w, 951 s
	Class B				
CrO_2Cl_2	Gas	990, 1000 [b]			
CrO_2F_2	,,	1006, 1016 [b]			

* acac = acetylacetone, mal = malonate, ox = oxalate.
† s = strong, sh = sharp, b = broad, m = medium, w = weak.
[a] Ref. 4. [b] Ref. 8.

The results fall into two groups. One corresponds to compounds generally regarded as containing double bonds, and the other consists of tetrahedral anions in which the bond order is intermediate between 1 and 2. The vibrational mode observed in tetrahedral anions is not a simple metal–oxygen stretching frequency but is triply degenerate, and any

[9] Byström, Wilhelmi, and Brotzen, *Acta. Chem. Scand.*, 1950, **4**, 1119.
[10] Palmer, *J. Amer. Chem. Soc.*, 1938, **60**, 2360.
[11] Byström and Wilhelmi, *Acta. Chem. Scand.*, 1950, **4**, 1131.
[12] Andersson and Magnelli, *Acta. Chem. Scand.*, 1950, **4**, 793.
[13] Jones, *Spectrochim. Acta*, 1958, **10**, 395.

slight distortion from tetrahedral symmetry could lead to the broad bands actually observed. The values of the force constants are surprisingly constant and support the idea

TABLE 2. *Stretching force constants.*

Bond	V–O	V–O	U–O	Cr–O	Cr–O	Mo–O	Mn–O	V–O
Compound	$VOCl_3$	$VOSO_4$	$UO_2(ClO_4)_2$	CrO_2F_2	CrO_4^{2-}	MoO_4^{2-}	MnO_4^-	VO_4^{3-}
Force constant (mdynes/Å)	7·55	7·25	7·75	7·5	5·48	5·66	5·50	4·86
Ref.	*a*	*b*	*c*	*d*	*e*	*f*	*g*	*h*

[a] Eichhoff and Weigel, *Z. anorg. Chem.*, 1954, **275**, 267. [b] Calc. from a frequency of 987 cm.$^{-1}$ for the diatomic ion VO^{2+}. [c] Jones and Penneman, *J. Chem. Phys.*, 1953, **21**, 542. [d] Calc. from data in ref. 8. [e] Stammreich, Bassi, and Sala, *Spectrochim. Acta*, 1958, **12**, 403. [f] Siebert, *Z. anorg. Chem.*, 1954, **275**, 225.

that a characteristic frequency is to be expected for each group, especially as the changes in reduced mass of an (M–O) group are also small, going from 12·3 for a Ti–O group to 15·0 for a U–O group. Treatments in terms of group frequencies are necessarily approximate but we feel that this work will be of diagnostic value in metal compounds. At least, if there is no band in the 900—1100 cm.$^{-1}$ region, one can be confident that there is no Metal=O bond in the compound; on the other hand when a band is observed in this region, it is good evidence for a Metal=O link, provided that there is not present in the molecule any other atom (*e.g.*, nitrogen) of similar atomic weight, which might give rise to a similar frequency.

Experimental.—Samples were laboratory reagents or were prepared according to published methods. The spectra were recorded on a Grubb-Parsons G.S.2A double-beam spectrometer.

We thank the University of Melbourne for a scholarship (to C. G. B.), and Dr. L. J. Bellamy for criticism.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1. [*Received, June 2nd*, 1959.]

---

714. *The Preparation and Reactions of Some Optically Active Substituted Benzhydrols.*

By R. T. PUCKOWSKI and W. A. ROSS.

The resolution of 2-, 3-, and 4-nitro-, 3,5-dinitro-, and 3-bromo-benzhydrol and the preparation of some optically active aminobenzhydrols are described. Some reactions of the alcohols and their esters involving unimolecular alkyl–oxygen fission have been investigated.

THE reactivity of diaryl secondary alcohols and their derivatives has been extensively studied by Kenyon and his collaborators [1] in connexion with alkyl–oxygen heterolysis. Their work included the effect of electron-releasing substituents (*e.g.* 4-methoxy).[2] Nitro- and amino-benzhydrols were of interest in this connexion, the latter also because they might offer a convenient route to other substituted benzhydrols.

2-Nitrobenzhydrol, prepared from 2-nitrobenzaldehyde, was resolved into its optically active forms by crystallisation of its cinchonidine succinate. It was reduced by sodium polysulphide or hydrogen and Adams catalyst, to 2-aminobenzhydrol with varying amounts of 2,2′-bis-α-hydroxybenzylazoxybenzene. The (—)-2-amino-compound gave an *N*-acetyl derivative; with cyanic acid it gave the (—)-2-ureido-alcohol and thence, by cyclis-

[1] Davies, Edwin, Kenyon, and Walsh, *J.*, 1957, 3158.
[2] Balfe, Doughty, Kenyon, and Poplett, *J.*, 1942, 605.

ation, 1,2,3,4-tetrahydro-3-oxo-1-phenylquinazoline. 3- and 4-Aminobenzhydrol were also prepared in active forms, as was the 3,5-dinitro-alcohol. 3-Bromobenzhydrol, prepared from 3-nitrobenzophenone by way of 3-aminobenzophenone, was similarly resolved.

The optical purity of some of these compounds was verified by a series of interconversions. Hydrogen sulphide reduced (−)-3,5-dinitrobenzhydrol to (−)-3-amino-5-nitrobenzhydrol. This was converted into (−)-3-aminobenzhydrol having the same specific rotation as when obtained by direct resolution, and, *via* (−)-3-bromo-5-nitrobenzhydrol, into (−)-3-bromo-benzhydrol of rotation similar to that of the alcohol obtained by resolution of the racemate. (+)-3-Amino- afforded (+)-3-bromo-benzhydrol with numerically the same specific rotation. (+)-2-Amino- afforded (+)-2-chloro-benzhydrol (this compound had previously been partially resolved [3]). Attempts to prepare 4-halogeno-benzhydrols from the 4-amine by the Sandmeyer reaction failed because of the instability of the latter in acid media.[4] It was shown that reduction of nitro- to amino-benzhydrols did not cause racemisation by re-oxidation of (+)-3-amino- to (+)-3-nitro-diphenylmethyl acetate by trifluoroperacetic acid.

The tendency of the alcohols and their esters to react by unimolecular alkyl–oxygen heterolysis was investigated by studying (*a*) hydrolysis of the optically active esters, (*b*) solvolytic reactivity in methanol, acetic acid, and formic acid, and (*c*) reactivity towards toluene-*p*-sulphinic acid.

The optically active hydrogen phthalates of 3- and 4-nitro-, 3,5-dinitro-, and 3-bromo-benzhydrol, and the hydrogen succinate of 2-nitrobenzhydrol were hydrolysed by ethanolic sodium hydroxide, and the unpurified alcohols obtained were reconverted into the ester whose specific rotations were within 2% of the original values.

The optically active hydrogen phthalates of 3- and 4-nitro-, 3,5-dinitro-, and 3-bromo-benzhydrol, on hydrolysis in 0·2N-sodium hydroxide at room temperature, yielded the optically active alcohols without observable racemisation. No neutral dialkyl phthalate was formed, but from the 4-nitro-ester. 4,4′-Dibenzoylazoxybenzene was also isolated.

The same four optically active hydrogen phthalates and that of the 2-nitro-alcohol, and acetic esters of 3-amino- and 3- and 4-acetamido-benzhydrol, were hydrolysed to the alcohols by an excess of 10% aqueous sodium carbonate under reflux. Only in the last three cases was racemisation observable, the isolated alcohols having optical purities of 90·2%, 92·2%, and 71·5% respectively.

The amino-, acetamido-, and mononitro-alcohols, the hydrogen phthalates of the nitro-alcohols and the bromo-alcohol, and the acetic esters of 3- and 4-nitro- and 4-acetamido-benzhydrol did not react with boiling absolute methanol or suffer thereby observable loss of optical activity. All these alcohols and esters, except 4-aminobenzhydrol, showed a similar lack of reactivity towards boiling 70% aqueous methanol. Both racemic and optically active 4-aminobenzhydrol gave the optically inactive anhydro-form [4] in 40% yield.

The hydrogen phthalates of 3- and 4-nitro-, 3,5-dinitro-, and 3-bromo-benzhydrol, and the hydrogen succinate of 2-nitrobenzhydrol, were unaffected by boiling glacial or 70% acetic acid. These optically active and racemic phthalates with hot 98% formic acid yielded the racemic formates and phthalic acid nearly quantitatively, but the optically active hydrogen phthalate of 2-nitrobenzhydrol, as well as the hydrogen succinate, acetate, and free alcohol, yielded 1,2-di-*o*-nitrophenyl-1,2-diphenylethylene.

The hydrogen phthalates of 3- and 4-nitro-, 3,5-dinitro-, and 3-bromobenzhydrol did not yield sulphones with sodium toluene-*p*-sulphinate in a slight excess of 0·2N-sodium hydroxide, but were hydrolysed at room temperature (the bromo-ester required heating on a water-bath). The hydrogen succinate of 2-nitrobenzhydrol remained unchanged after 12 hr. at 80°. The alcohols obtained from the optically active esters

[3] Balfe, Downer, Evans, Kenyon, Poplett, Searle, and Tárnoky, *J.*, 1946, 797.
[4] Cf. Kippenberg, *Ber.*, 1897, **30**, 1136.

of 3- and 4-nitro- and 3,5-dinitrobenzhydrol showed no significant loss in optical activity. The hydrogen phthalates of 3- and 4-nitro- and 3-bromo-benzhydrol, and the acetates of 4-acetamido- and 3-bromobenzhydrol with sodium toluene-*p*-sulphinate in formic acid yielded the corresponding *p*-tolyl sulphones and phthalic acid. The optically active hydrogen phthalates of 4-nitro- and 3-bromo-benzhydrol, and acetate of the 4-acetamido-alcohol, yielded racemic sulphones. The sulphone from 3-nitrobenzhydrol was also prepared by treating (±)-3-nitrodiphenylmethyl chloride with sodium toluene-*p*-sulphinate in ethanol. The optically active 4-acetamido-acetate with sodium toluene-*p*-sulphinate in 50% aqueous ethanol containing 0·2N-sodium hydroxide gave the racemic *p*-tolyl sulphone and the free 4-acetamido-alcohol showing 23% loss of optical activity.

Although the alcohols (except the 2- and 3-acetamido-compounds) did not react with sodium toluene-*p*-sulphinate in 60% aqueous ethanol, nearly quantitative yields of racemic *p*-tolyl sulphones were obtained from the 2- and 4-amino- and 4-acetamido-alcohols when sodium toluene-*p*-sulphinate was replaced by free toluene-*p*-sulphinic acid. Under these conditions none of the other alcohols reacted, even on prolonged heating at 80°. The racemic 2-amino-sulphone was also obtained by the interaction of the optically active alcohol with toluene-*p*-sulphinic acid in dilute hydrochloric acid. This sulphone with acetic anhydride yielded the 2-acetamido-sulphone; acetylation of the 4-amino-sulphone gave the same product as was obtained by treating 4-acetamidobenzhydrol with toluene-*p*-sulphinic acid in 60% aqueous ethanol.

From the above results, the following order of reactivity towards alkyl–oxygen heterolysis is obtained for benzhydrols: 4-NH_2 > 2-NH_2, 4-NHAc ≫ 3-NH_2, 3-NHAc, 3-Br > 2-, 3-, 4-NO_2, 3,5-$(NO_2)_2$.

The resistance of the nitrobenzhydrols and their esters to alkyl–oxygen heterolysis may be ascribed to the considerable inductive and mesomeric effects of this electron-attracting substituent, which decreases the electron-availability at the alkyl-carbon atom, particularly in the conjugated *ortho*- and *para*-position. This electron-withdrawal by the nitrophenyl group far outweighs the relatively weaker conjugative electron-release to the alkyl-carbon atom by the unsubstituted phenyl group of the benzhydrol molecule. The low solvolytic reactivity of *meta*-substituted benzhydrol and its esters suggests that the inductive effect of the nitro-group is sufficient alone to depress the tendency to alkyl–oxygen heterolysis.

Halogen in *ortho*- or *para*-substituted benzhydrols can exert its electron-releasing mesomeric effect, with consequent increase in electron-availability at the alkyl-carbon atom, and thus may facilitate the heterolysis of the alkyl-carbon–oxygen bond. The tendency of 2-chlorobenzhydrol to alkyl–oxygen heterolysis has previously been demonstrated.[3] The *meta*-halogenobenzhydrols, on the other hand, may be expected to show little tendency to undergo alkyl–oxygen heterolysis as only the adverse inductive effect is operative. The results with 3-bromobenzhydrol support this view.

A pronounced tendency to alkyl–oxygen heterolysis comparable to that of the alkoxybenzhydrols[2] may be expected in benzhydrols substituted with *ortho*- and *para*-amino-groups, in view of the strong electron-releasing mesomeric effect of these substituents. 4,4′-Bisdimethylaminobenzhydrol has been shown[5] to give the phenyl sulphone with sodium benzenesulphinate, to alkylate the active methylene groups in, *e.g.*, ethyl acetoacetate, and to react with other compounds in which the diphenylmethyl cation can displace a proton.[6,7] The results obtained confirm the marked reactivity of benzhydrols with *ortho*- and, particularly, *para*-amino- and -acetamido-groups, in contrast to the relatively unreactive *meta*-compounds. An analogy may be drawn here with the monomethoxybenzhydrols:[2,3] only the *p*-amino-alcohol reacted in aqueous methanol, probably by alkyl–oxygen heterolysis, yielding the polymeric anhydro-form instead of the expected methyl ether. The lower reactivity of the *ortho*-amino-alcohol may be compared with a

[5] Hinsberg, *Ber.*, 1917, **50**, 468.
[6] Möhlau and Heinze, *Ber.*, 1902, **35**, 361.
[7] Humphries, *J.*, 1926, 374.

similar observation for the methoxybenzhydrols,[8] attributed to the more effective contribution of the deactivating inductive effect from the *ortho*- than from the *para*-position. In the case of the amino-alcohol a contributory factor may also be a partial inhibition of the electron-releasing mesomeric effect of the *o*-amino-group due to its restricted ability to assume co-planarity with the ring, or possibly to intramolecular hydrogen-bonding between the amino- and the hydroxy-group.

Experimental

Unless otherwise stated, light petroleum refers to the fraction of b. p. 60—80°. Polarimetric measurements were made in a 4 dcm. tube.

(±)-2-*Nitrobenzhydrol*.—This alcohol, m. p. 63—64° on crystallisation from carbon disulphide (Hey and Mulley [9] give m. p. 59—60°), was prepared (82%) from phenylmagnesium bromide and *o*-nitrobenzaldehyde [10] (Found: C, 68·1; H, 4·8; N, 6·1. Calc. for $C_{13}H_{11}O_3N$: C, 68·1; H, 4·9; N, 6·1%). The *acetate*, prepared (77%) by using acetyl chloride and pyridine, had b. p. 149—151°/0·1 mm., n_D^{25} 1·5728 (Found: C, 66·5; H, 4·8; N, 5·0. $C_{15}H_{13}O_4N$ requires C, 66·4; H, 4·8; N, 5·2%). The *benzoate* (85%), m. p. 92—93°, crystallised in pale yellow prisms from ethanol (Found: C, 72·0; H, 4·6; N, 4·1. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5; N, 4·2%).

The *hydrogen phthalate* prepared by heating the alcohol with phthalic anhydride (1 mol.) and pyridine (1 mol.) crystallised in needles, m. p. 178° (decomp.), from ethyl acetate [Found: C, 66·5; H, 4·4; N, 3·6%; *M* (by titration with NaOH), 375. $C_{21}H_{15}O_6N$ requires C, 66·8; H, 4·0; N, 3·7%; *M*, 377].

(±)-2-Nitrobenzhydrol (0·8 g.) in 98% formic acid (3 ml.) deposited in 24 hr. yellow prismatic crystals (0·4 g.), m. p. 126—127°. Crystallised from ethyl acetate, 1,2-*di*-o-*nitrophenyl*-1,2-*diphenylethylene* (0·3 g.) had m. p. 127° (Found: C, 73·7; H, 4·4; N, 6·5. $C_{26}H_{18}O_4N_2$ requires C, 73·9; H, 4·3; N, 6·6%). This product (0·4 g.) with chromic oxide (0·4 g.) in 90% acetic acid (11 ml.) gave, after purification and crystallisation from ethanol, 2-nitrobenzophenone (0·3 g.), m. p. 105° (Hey and Mulley [9] give m. p. 105°). A similar product was obtained by the action of formic acid on the (±)-acetate, (±)- and (−)-hydrogen phthalate, and (±)-hydrogen succinate.

Resolution. The alcohol (22·9 g.), succinic anhydride (10·0 g.), and pyridine (8·7 g.) were heated on a steam-bath for 1 hr. The product was dissolved in acetone (80 ml.), 5N-hydrochloric acid (40 ml.) and then ice-water (200 ml.) were added, the precipitated oil giving a yellow solid (32 g.), m. p. 128—129°. Two crystallisations from ethyl acetate–light petroleum gave the *hydrogen succinate* (85%), m. p. 131°, pale yellow needles [Found: C, 62·0; H, 4·8; N, 4·2%; *M* (by titration with NaOH), 328. $C_{17}H_{15}O_6N$ requires C, 62·0; H, 4·6; N, 4·3%; *M*, 329].

To the succinate (101 g.) in ethyl acetate (500 ml.) cinchonidine (88·2 g.) was added in small quantities with warming and stirring. The filtered solution deposited two crops of crystals (78 and 20 g.), both of m. p. 126—128°, after 6 and 16 days at room temperature. Seven crystallisations from ethyl acetate gave the last two crops of cinchonidine salt, m. p. 129—130°, which with acid, yielded (+)-2-*nitrodiphenylmethyl hydrogen succinate* of identical rotatory powers. This ester (29·8 g.) had m. p. 69—70°, $[\alpha]_D^{20}$ +99·5° (*c* 3·0 in ethanol) (Found: C, 61·8; H, 4·8; N, 4·4%).

The more soluble cinchonidine salt was decomposed with dilute hydrochloric acid, and the liberated ester was purified (sodium hydrogen carbonate extraction and charcoal), giving a product (47 g.), m. p. 68—85°, $[\alpha]_D^{19}$ −60·2° (*c* 3·0 in ethanol). This in ethyl acetate–light petroleum, when seeded with the (±)-ester, gave, in seven days at 0° practically pure racemic ester (20 g.). Evaporation of the filtrate under reduced pressure gave the (−)-*ester* (26·8 g.), $[\alpha]_D^{20}$ −95·7° (*c* 3·1 in ethanol), as a pale yellow oil which did not solidify [Found: *M* (by titration with NaOH), 326].

To the (+)-ester (20 g.) in ethanol (100 ml.), sodium hydroxide solution (5·1 g. in 20 ml.) was added. After 48 hr. at room temperature, the product was heated to 80° for 1 hr. Water

[8] Davies and Kenyon, *Quart. Rev.*, 1955, **9**, 203.
[9] Hey and Mulley, *J.*, 1952, 2276.
[10] Newman and Smith, *J. Org. Chem.*, 1948, **13**, 596.

(150 ml.) was added to dissolve sodium succinate, and the (−)-*alcohol* which separated was extracted with ether. The ethereal solution was washed successively with sodium hydroxide solution, hydrochloric acid, and water. After evaporation of the dried (Na_2SO_4) ethereal solution the residue was distilled (b. p. 138—140°/0·1 mm.), giving a pale yellow oil (11·8 g.),

Specific rotatory power of (−)-2-*nitrobenzhydrol* (*l*, 1; *t*, 20°).

Solvent	Wavelength (Å) 6438	5893	5461	5086	4800	*c*
C_5H_5N	—	45·6°	—	85·5°	107°	2·047
$MeNO_2$	—	45·5	66·7°	89·0	105	2·029
EtOH	44·6°	66·2	83·4	109	150	2·092
C_6H_6	—	79·8	104	137	178	2·089
$CHCl_3$	—	95·4	136	172	219	2·054
CS_2	—	189	255	330	420	2·010

n_D^{25} 1·6077 (cf. Table) (Found: C, 68·0; H, 4·9; N, 6·0. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·9; N, 6·1%).

The (−)-alcohol gave the (+)-*hydrogen phthalate*, m. p. 127°, $[\alpha]_D^{19}$ +95·9° (*c* 2·0 in ethanol), colourless needles from benzene–light petroleum (Found: C, 66·6; H, 4·3; N, 3·8. $C_{21}H_{15}O_6N$ requires C, 66·8; H, 4·0; N, 3·7%).

Obtained similarly from the (−)-succinate, the (+)-*alcohol* had b. p. 141—143°/0·15 mm., n_D^{25} 1·6082, $[\alpha]_D^{20}$ +65·88° (*c* 4·0 in ethanol). This product gave the (−)-*benzoate* (60%), b. p. 192—194°/0·1 mm., n_D^{25} 1·6095, $[\alpha]_D^{19}$ −183·2° (*c* 4·5 in chloroform) (Found: C, 71·9; H, 4·6; N, 4·0. $C_{20}H_{14}O_4N$ requires C, 72·1; H, 4·5; N, 4·2%).

(±)-3-*Nitrobenzhydrol*.—This alcohol, m. p. 68—69°, was prepared (95%) by reduction of 3-nitrobenzophenone with aluminium isopropoxide. The *acetate* (92%), m. p. 78°, crystallised in pale yellow prisms from aqueous ethanol (Found: C, 66·2; H, 4·8; N, 5·3. $C_{15}H_{13}O_4N$ requires C, 66·4; H, 4·8; N, 5·2%). The *benzoate* (80%), m. p. 70—71°, crystallised in colourless needles from ethanol (Found: C, 72·0; H, 4·6; N, 4·0. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5; N, 4·2%). The *hydrogen succinate* (84%), m. p. 106°, formed colourless needles from benzene–light petroleum (Found: C, 62·2; H, 4·7; N, 4·4. $C_{17}H_{15}O_6N$ requires C, 62·0; H, 4·6; N, 4·3%). 3-*Nitrodiphenylmethyl chloride* (69%), b. p. 152—154°/0·3 mm., n_D^{25} 1·6084, was obtained by the interaction of the alcohol with thionyl chloride and pyridine at −10° (Found: C, 62·8; H, 4·3; N, 5·3; Cl, 14·0. $C_{13}H_{10}O_2NCl$ requires C, 63·0; H, 4·1; N, 5·6; Cl, 14·3%).

Resolution. 3-Nitrobenzhydrol (49 g.) was heated with phthalic anhydride (31·7 g.) and pyridine (23 g.) on a water-bath for 1½ hr., cooled, dissolved in acetone (150 ml.), and treated with 5N-hydrochloric acid (60 ml.) followed by ice-water (300 ml.). The (±)-*hydrogen phthalate* (73 g.) crystallised from ethyl acetate–light petroleum in colourless needles, m. p. 150—150·5° [Found: C, 66·9; H, 4·2; N, 3·7%; *M* (by titration with NaOH), 376. $C_{21}H_{15}O_6N$ requires C, 66·8; H, 4·0; N, 3·7%; *M*, 377].

Cinchonine (63·6 g.) was added in portions, with warming and stirring, to a solution of the (±)-phthalate (83·2 g.) in ethanol (350 ml.). The filtered solution, in 6 weeks, deposited a salt (69·3 g.), m. p. 158°, which was recrystallised six times to constant m. p. 175° and $[\alpha]_D^{20}$ +104° (*c* 2·0 in chloroform). Decomposition with hydrochloric acid and three crystallisations from ethyl acetate–light petroleum gave the (+)-*hydrogen phthalate* (43%), m. p. 136°, needles, $[\alpha]_D^{20}$ +15·4° (*c* 5·1 in chloroform) (Found: C, 66·9; H, 4·1; N, 3·8%).

The mother-liquors, on decomposition and removal of the cinchonine, gave a residue (41 g.), which crystallised from ethyl acetate–light petroleum. The filtrate from the first crop (21 g. of almost completely racemic ester) was diluted with light petroleum, and the crude product (35%) was recrystallised thrice from ethyl acetate–light petroleum, giving the (−)-*phthalate*, m. p. 136—137°, $[\alpha]_D^{20}$ −15·5° (*c* 3·6 in chloroform) [Found: *M* (by titration with NaOH), 374. $C_{21}H_{15}O_6N$ requires *M*, 377].

The (+)-hydrogen phthalate with 98% formic acid at 100° for 2 hr. gave the (±)-*formate* (73%), b. p. 154—156°/0·1 mm., n_D^{25} 1·5884 (Found: C, 65·4; H, 4·4; N, 5·3. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3; N, 5·5%). With sodium toluene-*p*-sulphinate (1·07 g.) in 98% formic

acid (7 ml.) at 100° for 3 hr. the (+)-hydrogen phthalate (1·13 g.) yielded (±)-*3-nitrodiphenylmethyl* p-*tolyl sulphone* (0·52 g., 51%), m. p. 133°, pale yellow prisms from aqueous ethanol (Found: C, 65·6; H, 4·7; S, 8·4. $C_{20}H_{17}O_4NS$ requires C, 65·4; H, 4·7; S, 8·7%). An identical product (62%) was obtained by heating (±)-3-nitrodiphenylmethyl chloride with sodium toluene-*p*-sulphinate in ethanol under reflux for 2 hr.

Hydrolysis of the (+)-phthalate (10 g.) with ethanolic sodium hydroxide gave a solid (5·9 g.) which, crystallised from aqueous ethanol, gave colourless needles of the (+)-*alcohol*, m. p. 92° (Found: C, 68·2; H, 4·8; N, 6·1. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·9; N, 6·1%) (cf. Table). This gave the (+)-*acetate* (88%), b. p. 162—164°/0·2 mm., n_D^{25} 1·5734, $[\alpha]_D^{21}$ +49·5° (*c* 2·1 in chloroform) (Found: C, 66·1; H, 4·7; N, 5·2. $C_{15}H_{13}O_4N$ requires C, 66·4; H, 4·8; N, 5·2%).

Specific rotatory power of (+)-*3-nitrobenzhydrol* (*l*, 1; *t*, 20°).

Solvent	Wavelength (Å) 5893	5461	5086	4800	*c*
$MeNO_2$	48·9°	62·0°	79·5°	102°	2·064
EtOH	58·1	69·8	81·4	96·4	2·064
$CHCl_3$	64·2	—	90·1	112	2·010
C_6H_6	65·8	79·6	91·3	110	2·036
C_5H_5N	76·9	96·6	117	142	2·133
CS_2	100	126	162	200	1·020

The (−)-alcohol, obtained similarly, had m. p. 92°, $[\alpha]_D^{20}$ −64·0° (*c* 1·9 in chloroform).

(±)-*4-Nitrobenzhydrol.*—This alcohol, m. p. 76—78°, was prepared (88%) by reduction of 4-nitrobenzophenone with aluminium isopropoxide. The *acetate* (91%), m. p. 88—89°, crystallised in colourless needles from ethanol (Found: C, 66·2; H, 4·9; N, 5·5. $C_{15}H_{13}O_4N$ requires C, 66·4; H, 4·8; N, 5·2%). The *hydrogen phthalate* (90%), m. p. 158°, crystallised in colourless needles from benzene [Found: C, 66·5; H, 4·0; N, 4·0%; *M* (by titration with NaOH), 376. $C_{21}H_{15}O_6N$ requires C, 66·8; H, 4·0; N, 3·7%; *M*, 377].

Resolution. To the (±)-phthalate (106 g.) in ethanol (1 l.) quinine (90·4 g.) was added in small quantities with warming and stirring. After filtration and storage for 2 days, the crystals (86 g.) were filtered off and recrystallised from ethanol. The salt (64 g.), m. p. 137—139°, obtained was decomposed by acid in the usual way, giving (+)-*4-nitrodiphenylmethyl hydrogen phthalate* (33 g.), m. p. 131—132°, $[\alpha]_D^{20}$ +37·2° (*c* 4·0 in chloroform), after crystallisation from benzene (Found: C, 66·5; H, 4·0; N, 3·8%). This ester, on reaction with formic acid, gave (±)-*4-nitrodiphenylmethyl formate* (80%), b. p. 153—154°/0·1 mm., n_D^{25} 1·6059 (Found: C, 65·2; H, 4·2; N, 5·5. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3; N, 5·5%). On reaction with sodium toluene-*p*-sulphinate in formic acid, the (+)-phthalate yielded (±)-*4-nitrodiphenylmethyl* p-*tolyl sulphone* (49%), b. p. 173—176°/0·1 mm. (Found: C, 64·8; H, 4·9; N, 3·2; S, 8·4. $C_{20}H_{17}O_4NS$ requires C, 65·4; H, 4·7; N, 3·8; S, 8·7%).

Recovery of the partially optically active phthalate from the mother-liquors from the resolution proved difficult. Hydrolysis of the crude phthalate gave, in varying yields, *4,4′-dibenzoylazoxybenzene*, m. p. 199—200°, pale yellow plates from benzene (Found: C, 76·9; H, 4·6; N, 7·0. $C_{26}H_{18}O_3N_2$ requires C, 76·8; H, 4·5; N, 6·9%). The *dioxime*, m. p. 220—221° (decomp.), crystallised as yellow needles from aqueous ethanol (Found: C, 71·8; H, 5·0; N, 12·4. $C_{26}H_{20}O_3N_4$ requires C, 71·6; H, 4·6; N, 12·8%). To more of the (±)-phthalate (26·0 g.) in 1 : 2 aqueous acetone (200 ml.) cinchonidine (20·3 g.) was added. After three weeks the salt (23 g.) obtained, m. p. 118—121°, was filtered off, and recrystallised thrice from 1 · 10 aqueous acetone. Decomposition of the final crop (11 g.), m. p. 120—122°, in the usual way, gave the (−)-*hydrogen phthalate* (5·1 g.), m. p. 130—131°, $[\alpha]_D^{20}$ −37·3° (*c* 4·4 in chloroform), after crystallisation from benzene–light petroleum [Found: *M* (by titration with NaOH), 377. $C_{21}H_{15}O_6N$ requires *M*, 377].

Hydrolysis of the (+)- and the (−)-hydrogen phthalate in the usual way gave the (+)-*alcohol*, m. p. 80—81° (cf. Table), pale yellow prisms from benzene (Found: C, 68·2; H, 4·9; N, 6·3. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·9; N, 6·1%), and the (−)-*alcohol*, m. p. 80—81°, $[\alpha]_D^{20}$ −77·9° (*c* 2·3 in chloroform), pale yellow prisms from benzene (Found: C, 68·1; H, 4·9; N, 6·2%).

Specific rotatory power of (+)-*4-nitrobenzhydrol* (*l*, 1; *t*, 19°).

Solvent	Wavelength (Å) 5893	5461	5086	4800	*c*
EtOH	50·7°	69·1°	78·0°	86·3°	1·995
C_5H_5N	56·8	69·3	85·3	103	2·005
$MeNO_2$	58·5	69·9	86·3	104	2·017
C_6H_6	74·9	93·9	110	128	2·002
$CHCl_3$	78·2	95·2	114	145	2·060
CS_2	117	150	185	208	2·013

(±)-*3,5-Dinitrobenzhydrol*.—3,5-Dinitrobenzophenone (33 g.) was added to aluminium isopropoxide (17 g.) in isopropyl alcohol (100 ml.), and was heated under reflux with slow distillation (3 drops/min.) for 3 hr. Removal of the solvent and addition of water (150 ml.) and hydrochloric acid (50 ml.) gave an oil which was taken up in ether. The ethereal solution was washed with sodium hydroxide solution and dried (Na_2SO_4). The oil obtained on removal of the ether solidified (m. p. 96—98°). (±)-*3,5-Dinitrobenzhydrol* (32 g.), m. p. 101—101·5°, crystallised from carbon disulphide or benzene–light petroleum in pale yellow needles (Found: C, 56·8; H, 3·8; N, 10·2. $C_{13}H_{10}O_5N_2$ requires C, 56·9; H, 3·7; N, 10·2%). The *acetate* (92%), m. p. 95°, crystallised as pale yellow prisms from ethanol (Found: C, 56·9; H, 3·9; N, 8·9. $C_{15}H_{12}O_6N_2$ requires C, 57·0; H, 3·8; N, 8·9%). The *hydrogen succinate* (86%), m. p. 140°, crystallised as pale yellow prisms from benzene or ethanol (Found: C, 54·8; H, 3·8; N, 7·7. $C_{17}H_{14}O_8N_2$ requires C, 54·5; H, 3·8; N, 7·5%).

Resolution. (±)-3,5-Dinitrobenzhydrol (27·4 g.), phthalic anhydride (14·8 g.), and triethylamine (11·0 g.) were heated on a water-bath for 1 hr. The oil produced, after the usual procedure, soon solidified. The product was washed with water, dried, and crystallised from benzene, giving the *hydrogen phthalate* (38 g.), as needles, m. p. 182° [Found: C, 59·6; H, 3·4; N, 6·7%; *M* (by titration with NaOH), 420. $C_{21}H_{14}O_8N_2$ requires C, 59·7; H, 3·3; N, 6·6%; *M*, 422].

To a hot solution of the hydrogen phthalate (140 g.) in acetone (800 ml.), cinchonidine (97 g.) was added portionwise with stirring. After filtration and storage for 5 days, the crystals (118 g.), m. p. 166—169°, $[\alpha]_D^{20}$ −63·4° (*c* 3·0 in chloroform), were filtered off. Two recrystallisations from acetone gave the pure salt (80 g.), m. p. 170—171°, $[\alpha]_D^{19}$ −64·1° (*c* 3·0 in chloroform). Decomposition of this salt in the usual way gave the (+)-*hydrogen phthalate* (45·5 g.), colourless needles, m. p. 163°, $[\alpha]_D^{20}$ +15·9° (*c* 2·0 in acetone), after three recrystallisations from benzene (Found: C, 59·5; H, 3·4; N, 6·8%). On working up of the mother-liquors, the yield of (+)-phthalate became 65%. Reaction with formic acid gave the (±)-*formate* (88%), m. p 85—86°, colourless needles from ethanol (Found: C, 55·8; H, 3·4; N, 9·3. $C_{14}H_{10}O_6N_2$ requires C, 55·6; H, 3·3; N, 9·3%).

The mother-liquors, containing the more soluble salt, were treated with hydrochloric acid, and the liberated crude ester (68 g.), m. p. 155—160°, was crystallised from benzene, giving a crop (17·2 g.) of practically racemic hydrogen phthalate. The concentrated filtrate deposited the (−)-*hydrogen phthalate* (63%), colourless needles, m. p. 162—163°, $[\alpha]_D^{20}$ −15·8° (*c* 2·1 in acetone) [Found: *M* (by titration with NaOH), 419. $C_{21}H_{14}O_8N_2$ requires *M*, 420].

Hydrolysis of the (−)-hydrogen phthalate by aqueous sodium carbonate (10%) at 100° for 1½ hr. gave the (+)-*alcohol* (92%), m. p. 107° (cf. Table), pale yellow needles from benzene–light petroleum (Found: C, 57·3; H, 3·7; N, 10·2. $C_{13}H_{10}O_5N_2$ requires C, 56·9; H, 3·7; N, 10·2%). The (−)-*alcohol* produced similarly from the (+)-hydrogen phthalate, had m. p. 107°, $[\alpha]_D^{19}$ −63·4° (*c* 2·0 in ethanol).

Specific rotatory power of (+)-*3,5-dinitrobenzhydrol* (*l*, 1; *t*, 22°).

Solvent	Wavelength (Å) 5893	5461	5086	4800	*c*
$MeNO_2$	60·6°	73·5°	88·4°	107°	2·046
EtOH	63·6	76·2	91·9	112	2·013
C_5H_5N	83·6	—	—	—	1·986
$CHCl_3$	91·5	108	127	148	2·022
C_6H_6	135	165	197	231	2·004

(±)-3-*Bromobenzhydrol.*—This alcohol, m. p. 44°, was prepared from 3-nitrobenzophenone, *via* 3-aminobenzophenone (93%), Sandmeyer reaction (61%) and subsequent reduction (91%) by aluminium isopropoxide. The *acetate* (79%) had b. p. 138—140°/0·3 mm. (Found: C, 59·2; H, 4·5; Br, 25·8. $C_{15}H_{13}O_2Br$ requires C, 59·1; H, 4·3; Br, 26·2%).

Resolution. The alcohol (132 g.), phthalic anhydride (74 g.), and triethylamine (60 g.), by the usual procedure, gave, after crystallisation from acetic acid (90%) or ethyl acetate, the *hydrogen phthalate* (83%), m. p. 142° [Found: C, 61·6; H, 4·0; Br, 19·7%; *M* (by titration with NaOH), 409. $C_{21}H_{15}O_4Br$ requires C, 61·3; H, 3·7; Br, 19·4%; *M*, 411].

To the (±)-hydrogen phthalate (61·6 g.) in ethyl acetate (400 ml.), cinchonine (44·2 g.) was added portionwise with warming and stirring. After filtration and storage for 10 days, an impure dextrorotatory salt (59·4 g.), m. p. 154°, was deposited. Seven recrystallisations from ethyl acetate gave constant $[\alpha]_D^{20}$ +109·0° (*c* 3·6, *l* 2 in chloroform), m. p. 161°. Decomposition of this salt (10·6 g.) in the usual way gave the (+)-*hydrogen phthalate* (5·5 g.), m. p. 127°, $[\alpha]_D^{20}$ +14·95° (*c* 2·0 in chloroform), colourless needles (from ethyl acetate–light petroleum) [Found: C, 61·0; H, 3·9; Br, 19·2%; *M* (by titration with NaOH), 409]. This phthalate on treatment with formic acid gave the (±)-*formate* (78%), b. p. 117—119°/0·1 mm., n_D^{25} 1·5948 (Found: C, 58·0; H, 4·0; Br, 27·3. $C_{14}H_{11}O_2Br$ requires C, 57·8; H, 3·8; Br, 27·5%). Reaction of the (+)-hydrogen phthalate with sodium toluene-*p*-sulphinate in formic acid gave (±)-3-*bromodiphenylmethyl* p-*tolyl sulphone* (75%), m. p. 144°, cubic crystals from methyl acetate (Found: S, 7·9; Br, 19·7. $C_{20}H_{17}O_2SBr$ requires S, 8·0; Br, 19·9%). An identical product was obtained (90%) from (±)-3-bromodiphenylmethyl acetate and sodium toluene-*p*-sulphinate in formic acid.

The mother-liquors, containing the more soluble salt, were decomposed with hydrochloric acid, and the crude solid (24 g.) obtained, on crystallisation from ethyl acetate–light petroleum, yielded a crop (15·1 g.) of practically pure racemic ester. On cooling, the filtrate deposited the (−)-*hydrogen phthalate* (7·2 g.), m. p. 127°, $[\alpha]_D^{20}$ −14·8° (*c* 2·0 in chloroform), colourless needles from 90% acetic acid [*M* (by titration with NaOH), 408. $C_{21}H_{15}O_4Br$ requires *M*, 411]. The (−)-phthalate was also obtained from the (±)-hydrogen phthalate (32·9 g.) and cinchonine (23·5 g.) in acetone (120 ml.). The salt (25·8 g.), m. p. 154—155°, deposited after 5 days, was recrystallised six times from acetone, giving a product (5·5 g.), m. p. 160°. Decomposition of this salt gave a (−)-hydrogen phthalate (3·0 g.), m. p. 127°, $[\alpha]_D^{20}$ −15·1° (*c* 2·1 in chloroform).

Hydrolysis of the (+)-hydrogen phthalate gave the (+)-*alcohol* (92%), colourless needles (from ligroin), m. p. 56°, $[\alpha]_D^{18}$ +32·8° (*c* 2·1 in chloroform) (Found: C, 59·2; H, 4·4; Br, 30·0. $C_{13}H_{11}OBr$ requires C, 59·3; H, 4·2; Br, 30·4%). The (−)-*alcohol*, obtained similarly from the (−)-hydrogen phthalate, had m. p. 56°, $[\alpha]_D^{18}$ −32·4° (*c* 2·2 in chloroform).

2-*Aminobenzhydrol.*—A solution of sodium polysulphide from sodium sulphide (6·0 g.) and sulphur (1·5 g.) in water (20 ml.) was added dropwise to 2-nitrobenzhydrol (2·4 g.) in boiling ethanol (40 ml.), and the mixture was heated under reflux for 1 hr. Ethanol was removed under reduced pressure, 5N-hydrochloric acid (50 ml.) was added, sulphur was filtered off, and the solution was basified with aqueous ammonia. The precipitated oil solidified (1·3 g.; m. p. 110—112°), and on crystallisation from ethanol gave (±)-2-aminobenzhydrol (53%), colourless prisms, m. p. 116° (Gabriel and Stetzner,[11] by reduction of 2-aminobenzophenone, obtained a product, m. p. 120°). 1-α-*Hydroxybenzylphenylazo*-2-*naphthol*, prepared in the usual way, crystallised from acetic acid (90%) in dark red prisms, m. p. 159—160° (Found: C, 77·9; H, 5·1; N, 7·8. $C_{23}H_{18}O_2N_2$ requires C, 78·0; H, 5·1; N, 7·9%).

A solution of (±)-2-nitrobenzhydrol (2·0 g.) in ethanol (50 ml.), with Adams catalyst (0·10 g.), absorbed the theoretical quantity of hydrogen at room temperature and 5 atm. in 15 min. The filtered solution was concentrated and, on the addition of water, (±)-2-aminobenzhydrol (92%), m. p. 115—116°, crystallised. In a second experiment (with 4 g.), apart from aminobenzhydrol (0·8 g.), a neutral substance was isolated by ether-extraction from acid solution. The ethereal solution was washed with sodium hydroxide solution and dried (Na_2SO_4). After removal of the ether, the residue (2·8 g.) crystallised from methanol, giving colourless 2,2′-*di*-(α-*hydroxybenzyl*)*azoxybenzene* (1·8 g.), m. p. 150° (Found: C, 76·1; H, 5·5; N, 6·9. $C_{26}H_{22}O_3N_2$ requires C, 76·1; H, 5·4; N, 6·8%).

(+)-2-*Aminobenzhydrol*, prepared similarly (93%) from (+)-2-nitrobenzhydrol, crystallised from aqueous ethanol in prisms, m. p. 108°, $[\alpha]_D^{19}$ +2·72° (*c* 2·1 in chloroform), $[\alpha]_D^{20}$ −3·55° (*c* 2·0 in ethanol), $[\alpha]_D^{21}$ −25·9° (*c* 2·0 in N-hydrochloric acid) (Found: C, 78·0; H, 6·6; N, 7·1. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6; N, 7·0%). The (−)-*alcohol* prepared similarly had m. p.

108°, $[\alpha]_D^{20}$ −2·73° (*c* 2·0 in chloroform), $[\alpha]_D^{19}$ +3·6° (*c* 2·0 in ethanol). The (−)-alcohol (1·0 g.) in ethanol (8·5 ml.) was treated with sodium toluene-*p*-sulphinate (1·2 g.), followed by N-hydrochloric acid (5·6 ml.). After 24 hr. the product was filtered off, and crystallisation from aqueous ethanol gave (±)-2-*aminodiphenylmethyl* p-*tolyl sulphone* (88%), m. p. 163° (Found: C, 71·1; H, 5·9; N, 3·8; S, 9·4. $C_{20}H_{19}O_2NS$ requires C, 71·2; H, 5·7; N, 4·1; S, 9·5%). With acetic anhydride, this sulphone gave the (±)-2-*acetamido-compound* (77%), needles, m. p. 192—193° (from methanol) (Found: C, 69·9; H, 5·7; N, 3·6; S, 8·5. $C_{22}H_{21}O_3NS$ requires C, 699; H, 5·6; N, 3·7; S, 8·4%).

A mixture of (−)-2-aminobenzhydrol (1·0 g.) in ether (3 ml.) and acetic anhydride (0·56 g.) was heated on a water-bath for 10 min. After cooling and shaking with 5% sodium hydrogen carbonate solution (50 ml.), an oil was precipitated, which was taken up in ether. The ethereal solution was washed successively with N-sodium hydroxide solution, N-hydrochloric acid, and water, dried (Na_2SO_4), and evaporated. (−)-2-*Acetamidobenzhydrol* (80%) was obtained as a pale yellow oil, $[\alpha]_D^{20}$ −51·1° (*c* 2·0 in chloroform), which set to a glass. It decomposed on attempted distillation at 0·2 mm. (Found: C, 75·1; H, 6·5; N, 5·9. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·3; N, 5·8%).

A solution of sodium cyanate (0·78 g.) in water (5 ml.) was added to (−)-2-aminobenzhydrol (1·4 g.) in 5N-hydrochloric acid (5 ml.). A colourless oil was precipitated which solidified and was washed with sodium hydroxide solution and then with water. From aqueous ethanol (−)-2-*ureidobenzhydrol* (82%) crystallised in colourless plates, m. p. 165° (decomp.), $[\alpha]_D^{19}$ −52·4° (*c* 1·0 in methanol) (Found: C, 69·0; H, 5·8; N, 11·5. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8; N, 11·6%). Treatment with concentrated hydrochloric acid, gave (±)-1,2,3,4-tetrahydro-3-oxo-1-phenylquinazoline (87%), m. p. 197°, colourless prisms from aqueous ethanol (Gabriel and Stetzner [11] give m. p. 193°).

3-*Aminobenzhydrols.*—(±)-3-Aminobenzhydrol, m. p. 79°, was prepared by sodium polysulphide reduction (70%) or by reduction with Adams catalyst and hydrogen (90%) of the nitro-alcohol. Reduction of (±)-3-nitrodiphenylmethyl acetate by the latter method gave (±)-3-*aminodiphenylmethyl acetate* (70%), which did not crystallise (Found: C, 74·4; H, 6·5; N, 5·7. $C_{15}H_{15}O_2N$ requires C, 74·4; H, 6·3; N, 5·8%). Trifluoroacetic anhydride (5·2 g.) was added to a suspension of 86% w/w hydrogen peroxide solution (1·0 g.) in methylene chloride (40 ml.) cooled in ice. The mixture was stirred for 7 min. and the ice-bath removed. (±)-3-Aminodiphenylmethyl acetate (1·2 g.) in methylene chloride (15 ml.) was added dropwise in 10 min. with vigorous stirring. After being stirred for a further 10 min. the mixture was heated under reflux for 30 min. The cooled product was washed with water, N-sodium carbonate, and water. Removal of the solvent gave a pale yellow oil, which crystallised from aqueous ethanol, giving the (±)-3-nitro-acetate (74%), m. p. and mixed m. p. 77—78°.

(±)-3-*Acetamidobenzhydrol*, prepared as reported for the 2-isomer (78%), crystallised from ethanol in rhombs, m. p. 138° (Found: C, 74·7; H, 6·3; N, 5·7. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·3; N, 5·8%).

(+)-3-*Aminobenzhydrol*, obtained by reduction of the (+)-nitro-alcohol (88%), crystallised from aqueous ethanol in colourless prisms, m. p. 106°, $[\alpha]_D^{20}$ +16·76° (*c* 2·0 in chloroform), $[\alpha]_D^{20}$ +2·2° (*c* 1·9 in ethanol) (Found: C, 78·0; H, 6·8; N, 7·0. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6; N, 7·0%). The (−)-*alcohol* obtained similarly (86%) had m. p. 106°, $[\alpha]_D^{22}$ −16·5° (*c* 2·0 in chloroform). (+)-3-*Aminodiphenylmethyl acetate* (72%), obtained by reduction of the (+)-nitro-acetate, was a thick colourless oil, n_D^{25} 1·5894, $[\alpha]_D^{20}$ +5·55° (*c* 2·0 in chloroform), $[\alpha]_D^{20}$ +1·90° (*c* 3·10 in ethanol) (Found: C, 74·4; H, 6·6; N, 5·9. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·3; N, 5·8%). Oxidation with trifluoroperacetic acid gave the (+)-3-nitro-acetate (71%), b. p. 161—164°/0·2 mm., n_D^{25} 1·5730, $[\alpha]_D^{19}$ +48·8° (*c* 2·12 in chloroform). On acetylation, the (+)-3-amino-acetate gave the (+)-3-*acetamido-acetate* (74%), n_D^{25} 1·5851, $[\alpha]_D^{20}$ +7·84° (*c* 2·50 in chloroform) (Found: C, 71·8; H, 5·8; N, 5·0. $C_{17}H_{17}O_3N$ requires C, 72·1; H, 6·1; N, 4·9%). A similar product (77%) was obtained by the acetylation of (+)-3-acetamidobenzhydrol.

(+)-3-*Acetamidobenzhydrol*, prepared in the reported manner (80%), crystallised from ethanol in prisms, m. p.128°, $[\alpha]_D^{20}$ +10·7° (*c* 1·50 in chloroform) (Found: C, 74·8; H, 6·2; N, 5·7. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·3; N, 5·8%).

4-*Aminobenzhydrols.*—(±)-4-Aminobenzhydrol, m. p. 121°, was prepared (80%) by reduction of the nitro-alcohol with Adams catalyst and hydrogen. Similarly obtained (89%) from

[11] Gabriel and Stetzner, *Ber.*, 1896, **29**, 1304.

(+)-4-nitrobenzhydrol, (−)-4-*aminobenzhydrol* crystallised in colourless needles (from aqueous ethanol), m. p. 136—137°, $[\alpha]_D^{20}$ −30·3° (*c* 1·12 in chloroform), $[\alpha]_D^{19}$ −38·5° (*c* 2·01 in ethanol) (Found: C, 78·3; H, 6·7; N, 7·1. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6; N, 7·0%). On heating with 70% aqueous methanol for 10 hr. under reflux, the (−)-alcohol yielded the optically inactive anhydro-form (40%), which separated from ethanol as a yellow amorphous powder, m. p. 235—240° (Kippenberg [4] gives m. p. 220—225°) [Found: C, 85·6; H, 6·3; N, 7·3. Calc. for $(C_{13}H_{11}N)_x$: C, 86·2; H, 6·1; N, 7·7%]. Toluene-*p*-sulphinic acid in aqueous ethanol gave the p-*tolyl sulphone* (95%), m. p. 222°, colourless needles from ethanol (Found: C, 71·3; H, 5·9; S, 9·1. $C_{20}H_{19}O_2NS$ requires C, 71·2; H, 5·7; S, 9·5%). (−)-4-*Acetamidobenzhydrol*, prepared by the method used for the *ortho*-isomer (91%), crystallised from ethanol in colourless plates, m. p. 147°, $[\alpha]_D^{19}$ −16·7° (*c* 2·0 in ethanol) (Found: C, 75·0; H, 6·5; N, 5·7. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·3; N, 5·8%). Its (−)-*acetate* (78%) crystallised from aqueous ethanol or benzene–light petroleum in plates, m. p. 122°, $[\alpha]_D^{20}$ −41·3° (*c* 2·0 in ethanol) (Found: C, 72·3; H, 6·2; N, 4·7. $C_{17}H_{17}O_3N$ requires C, 72·1; H, 6·1; N, 4·9%).

This ester, when heated under reflux with an excess of 10% sodium carbonate solution for 3 hr., gave (−)-4-acetamidobenzhydrol, m. p. 143—145°, $[\alpha]_D^{20}$ −11·9° (*c* 2·0 in ethanol); the (−)-acetate obtained on re-esterification had m. p. 120—121°, $[\alpha]_D^{19}$ −30·1° (*c* 2·0 in ethanol). (−)-4-Acetamidobenzhydrol with toluene-*p*-sulphinic acid in aqueous ethanol gave the p-*tolyl sulphone* (83%), m. p. 213°, prisms from ethanol (Found: C, 69·9; H, 5·7; N, 3·5; S, 8·2. $C_{22}H_{21}O_3NS$ requires C, 69·6; H, 5·6; N, 3·7; S, 8·4%). An identical product was obtained (89%) by acetylation of (±)-4-aminodiphenylmethyl *p*-tolyl sulphone, and also (84%) from (−)-4-acetamidodiphenylmethyl acetate and sodium toluene-*p*-sulphinate and formic acid. (−)-4-Acetamidobenzhydrol (1·13 g.) in ethanol (10 ml.) was treated with sodium toluene-*p*-sulphinate (2·14 g.), followed by 0·2N-sodium hydroxide (10·0 ml.), and heated at 80° for 5 hr. Working up in the usual way gave (−)-4-acetamidobenzhydrol (65%), $[\alpha]_D^{20}$ −12·9° (*c* 2·1 in ethanol), and the *p*-tolyl sulphone (22%), m. p. and mixed m. p. 212—213° (from ethyl acetate).

3-*Amino-5-nitrobenzhydrol*.—A solution of (±)-3,5-dinitrobenzhydrol (5·0 g.) in ethanol (25 ml.) and aqueous ammonia (8 ml.; *d* 0·880) was cooled in ice and saturated with hydrogen sulphide. The product was heated under reflux for 25 min. and cooled. The saturation and heating were repeated twice, the ethanol was removed under reduced pressure, the residue shaken with 5N-hydrochloric acid (60 ml.), and the sulphur filtered off. The filtered (charcoal) solution was basified with aqueous ammonia, and the precipitated oil extracted with ether. After being washed with water, the dried (Na_2SO_4) solution was evaporated, leaving (±)-3-*amino-5-nitrobenzhydrol* (74%) as a glass (Found: C, 64·2; H, 4·3; N, 11·3. $C_{13}H_{10}O_3N_2$ requires C, 64·5; H, 4·2; N, 11·6%). (±)-3-*Benzamido-5-nitrobenzhydrol*, prepared in the usual way, crystallised from ethanol in pale yellow needles, m. p. 180° (Found: C, 68·9; H, 4·8; N, 7·9. $C_{20}H_{16}O_4N_2$ requires C, 69·0; H, 4·6; N, 8·0%). (−)-3-Amino-5-nitrobenzhydrol, prepared similarly (70%) from (−)-3,5-dinitrobenzhydrol, did not crystallise and had $[\alpha]_D^{19}$ −51·9° (*c* 1·0, *l* 2 in chloroform). This gave the (−)-N-*benzoate*, m. p. 174°, pale yellow needles (from ethanol), $[\alpha]_D^{22}$ −26·3° (*c* 2·1 in acetone) (Found: C, 68·7; H, 4·8; N, 8·0%).

(+)-2-*Chlorobenzhydrol*.—A solution (5 ml.) of sodium nitrite (0·85 g.) was added with stirring at 0—5° to a solution of (+)-2-aminobenzhydrol (2·2 g.) in concentrated hydrochloric acid (5 ml.) and water (10 ml.). The filtered product was added at 3° to a stirred solution of cuprous chloride (4·4 g.) in 3N-hydrochloric acid (40 ml.). Benzene (50 ml.) was added, and the mixture allowed to reach room temperature with vigorous stirring. After two hr., the product was heated at 80° for 30 min., and the benzene layer was separated and washed successively with water, sodium hydroxide solution, and water. After removal of the solvent, the residue (1·8 g.) was passed in benzene (25 ml.)–light petroleum (50 ml.) through alumina (1 × 10 cm.). The colourless oil (1·6 g.) obtained {$[\alpha]_D^{20}$ +19·8° (*c* 2·6 in ethanol)} did not solidify or crystallise, and was converted, in the usual way, into the (−)-*hydrogen phthalate* (82%), m. p. 140°, colourless needles (from benzene–ligroin), $[\alpha]_D^{20}$ −33·7° (*c* 1·0 in ethanol) [Found: C, 69·1; H, 4·3; Cl, 9·5%; *M* (by titration with NaOH), 364. $C_{21}H_{15}O_4Cl$ requires C, 68·7; H, 4·1; Cl, 9·7%; *M*, 366·7] (Balfe *et al.*[3] report m. p. 69—71°, $[\alpha]_D$ 15·6°, for the partially resolved compound). Hydrolysis of the (−)-phthalate with alcoholic sodium hydroxide solution gave (+)-2-*chlorobenzhydrol*, an oil, $[\alpha]_D^{19}$ +22·0° (*c* 2·0 in ethanol) (Found: Cl, 16·0. $C_{13}H_{11}OCl$ requires Cl 16·2%) (Balfe *et al.*[3] report m. p. 65°, $[\alpha]_D$ +4·7°, for the partially resolved compound). Reconversion of alcohol into the phthalate gave a product, m. p. 139—140°, $[\alpha]_D^{20}$ −32·7° (*c* 1·0 in ethanol).

(±)-2-Chlorobenzhydrol (68%), prepared from (±)-2-aminobenzhydrol and crystallised from ligroin, had m. p. 65—66°.

(+)-3-*Bromobenzhydrol*.—A solution (5 ml.) of sodium nitrite (1·47 g.) was added with stirring at 4° to (+)-3-aminobenzhydrol (3·98 g.) in sulphuric acid (2 ml.) and water (25 ml.). The filtered solution was added in three portions to a well-stirred solution of cuprous bromide (5·75 g.) in 48% hydrobromic acid (25 ml.) and water (50 ml.) at 0°. Working up as before gave a colourless (+)-3-bromobenzhydrol (61%), m. p. and mixed m. p. 55—56° (from ligroin), $[\alpha]_D^{18}$ +32·4° (*c* 2·3 in chloroform).

(−)-3-*Nitrobenzhydrol*.—A solution (5 ml.) of sodium nitrite (0·74 g.) was added at 0—3° to (−)-3-amino-5-nitrobenzhydrol (2·44 g.) in 3N-hydrochloric acid (40 ml.). 5·2N-Hypophosphorous acid (13·5 ml.) was added dropwise at 5° with vigorous stirring to the filtered product. The product was stirred for 4 hr. at room temperature and set aside for 18 hr. Working up as before and crystallisation from carbon disulphide–light petroleum, gave (−)-3-nitrobenzhydrol (54%), m. p. and mixed m. p. 91—92°, $[\alpha]_D^{19}$ −64·1° (*c* 2·1 in chloroform).

(−)-3-*Bromo-5-nitrobenzhydrol*.—A solution (5 ml.) of sodium nitrite (1·47 g.) was added at 0—5° to (−)-3-amino-5-nitrobenzhydrol (4·88 g.) in 48% hydrobromic acid (18 ml.) and water (20 ml.). Cuprous bromide (11·5 g.) in 48% hydrobromic acid (30 ml.) and water (60 ml.) was added with stirring at 3—5°. Benzene (120 ml.) was added, and stirring was continued at room temperature for 1 hr. and then at 50—60° for 3 hr. The benzene layer was washed with sodium hydroxide solution and water, and the solvent removed. The residue was distilled, giving (−)-3-*bromo-5-nitrobenzhydrol* (54%), b. p. 171—173°/0·15 mm., $[\alpha]_D^{22}$ −63·06° (*c* 6·5 in chloroform) (Found: Br, 25·7. $C_{13}H_{10}O_3NBr$ requires Br, 25·9%). The (−)-*hydrogen phthalate* (79%) crystallised as pale yellow rhombs, m. p. 143°, $[\alpha]_D^{19}$ −18·2° (*c* 0·5 in chloroform), from ethyl acetate–light petroleum [Found: Br, 17·2%; *M* (by titration with NaOH), 451. $C_{21}H_{14}O_6NBr$ requires Br, 17·5%; *M*, 456].

(−)-3-*Amino-5-bromobenzhydrol*.—A solution of (−)-3-bromo-5-nitrobenzhydrol (2·0 g.) in ethanol (50 ml.) with Adams catalyst (0·06 g.) absorbed the theoretical quantity of hydrogen at room temperature and 5 atm. in 8 min. The solvent was removed from the filtered solution, and the residue extracted with 2N-hydrochloric acid (15 ml.). The purified (charcoal) extract was neutralised with 2N-ammonia, and the precipitated oil extracted with ether. The ethereal solution was washed with water, dried (Na_2SO_4), and evaporated, leaving (−)-3-*amino-5-bromobenzhydrol* (83%), $[\alpha]_D^{22}$ −17·2° (*c* 2·2 in chloroform), which solidified but could not be crystallised (Found: N, 4·8; Br, 28·3. $C_{13}H_{12}ONBr$ requires N, 5·0; Br, 28·7%). Deamination of this alcohol by the method described gave (−)-3-bromobenzhydrol (58%), m. p. and mixed m. p. 56°, $[\alpha]_D^{20}$ −32·1° (*c* 2·0 in chloroform), $[\alpha]_D^{19}$ −56·6° (*c* 2·0 in carbon disulphide).

We thank Dr. J. F. McGhie for his interest and encouragement, Mr. F. X. Somm and Dr. A. F. LeC. Holding for assistance in the initial stages of this work, Laporte Chemicals Ltd. for a gift of hydrogen peroxide, and the Governors of Chelsea College of Science and Technology for a Research Assistantship (to R. T. P.).

Department of Chemistry, Chelsea College of Science and Technology,
London, S.W.3. [*Received, February 12th*, 1959.]

715. *The Catalytic Hydrogenation of Unsaturated Hydrocarbons. Part IV.*[1] *The Kinetics of the Hydrogenation of Acetylene over Supported and Unsupported Iron, Cobalt, and Copper, and over some Nickel–Cobalt and Nickel–Copper Alloys.*

By G. C. Bond and R. S. Mann.

At constant acetylene pressure, the rate of hydrogenation of acetylene over pumice-supported and unsupported iron and cobalt catalysts is proportional to the hydrogen pressure, and no evidence of a " two-rate " effect (of the type described for nickel in Part III [1]) has been found. Both types of copper catalyst do show this effect, but in contradistinction to nickel the activation energy E_A of the process operating at low hydrogen pressures is greater (*ca.* 20 kcal. mole^{-1}) than that (E_B) for the additional process at high hydrogen pressures (*ca.* 4 kcal. mole^{-1}). Values of E_A for iron, cobalt, and nickel are all close to 8·6 kcal. mole^{-1}, and the activity differences, which are substantial, therefore reside in the pre-exponential terms.

Mixed nickel–copper and nickel–cobalt oxides prepared from co-precipitated basic carbonates have been reduced to homogeneous alloy powders at 500°. In the nickel–cobalt system, the " two-rate " effect persists through to the composition 20Ni : 80Co, and E_A increases markedly with increasing cobalt concentration in the range 0—40% of cobalt. With nickel–copper, E_A is similarly raised by increasing copper concentration. Activity patterns are notably temperature-sensitive, and indicate that at high temperatures the *d*-band hole concentration determines the activity, but at low temperatures the situation is more complex. The results are discussed in terms of current concepts.

Part III [1] described an investigation of the kinetics of hydrogenation of acetylene over various types of nickel catalyst, and the same general rate expression

$$-\mathrm{d}p/\mathrm{d}t = k_A P_{H_2} + k_B(P_{H_2} - P_{H_2}^0) \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

fitted all the results. We can describe the phenomenon of a rate expression containing two rate constants as a " two-rate effect." Our first object was to extend the study of this reaction to metals lying near nickel in the Periodic Table, to see which others if any, showed this effect.

Sheridan's work [2] showed that iron and cobalt behaved similarly to, but were less active than, nickel. The reaction over copper is of course complicated by formation of cuprene, which Sheridan was able to overcome by using an excess of hydrogen. He was, however, unable to make reliable kinetic measurements over cobalt and copper owing to the deactivation of his catalysts. References to earlier work are given in Sheridan's paper.

A further object of this work was to investigate the kinetics of hydrogenation of acetylene over some alloy powders. Homogeneous binary alloys of metals occupying adjacent positions in the Periodic Table offer an excellent means of studying the relationship between the activity and the electronic constitution of the catalyst, since they often exhibit marked changes in both while the lattice dimensions scarcely alter. While the catalytic properties of the nickel–copper system have been quite widely studied, the literature reveals few such studies of the nickel–cobalt system.[3] The results for iron, cobalt, nickel,[1,4] and copper, together with the results on the nickel–copper and nickel–cobalt alloys, form a broad basis

[1] Part III, Bond and Mann, *J.*, 1958, 4738.
[2] Sheridan, *J.*, 1945, 470.
[3] Long, Frazer, and Ott, *J. Amer. Chem. Soc.*, 1934, **56**, 1101; Rienäcker and Unger, *Z. anorg. Chem.*, 1953, **274**, 47.
[4] Bond, *J.*, 1958, 2705 (Part I).

for evaluating the significance of the electronic factor in the hydrogation of acetylene, and cast further light on possible reaction mechanisms.

Experimental

The apparatus and procedure were essentially as described in Parts I [4] and III,[1] save that for some later experiments the reaction vessel was modified to allow the reduction of the catalyst in a hydrogen stream *in situ*.

Metal Catalysts.—Pumice-supported iron, cobalt, and copper catalysts containing about 10% of metal by weight were prepared by the standard method, starting from the nitrates; they are designated Fe–p, etc. The pumice-supported ferric and cobalt nitrate were each calcined in an oxygen stream for 10 hr. at 350° and reduced, in an external system, in a hydrogen stream for 20 hr. at 400°. The corresponding figures for the copper catalyst are: 6 hr. at 250° and 10 hr. at 300°.

These metals were also prepared as powders (Fe–I etc.) by reduction of the oxides derived from the basic carbonates, under conditions identical with those used in preparing nickel powder in this manner.[1] An iron powder (Fe–II) was also prepared by calcination of ferric nitrate (12 hr. at 350°) followed by reduction in a hydrogen stream (24 hr. at 400°). This and other catalysts not reduced in the reaction vessel were pretreated *in situ* in a static hydrogen atmosphere at the previously used reduction temperature for the following times: Fe–p, 20 hr.; Fe–II, 10 hr.; Co–p, 2 hr.; Cu–p, 14 hr.

Alloy Catalysts.—Homogeneous nickel–cobalt and nickel–copper alloy powders were prepared by Best and Russell's method;[5] the mixed basic carbonates, precipitated from solutions containing the appropriate quantities of the nitrates, were decomposed to the oxides, which were then reduced *in situ* in a hydrogen stream for 24 hr. at 500°.

The surface areas of the alloy and the metal powders were determined by low-temperature krypton adsorption in the laboratories of the Research Department, Imperial Chemical Industries Limited, Billingham Division; the *X*-ray spectra of the alloys and of the cobalt powder were also determined there.

Results

The designation of pressure–time curves is as in Parts I and III. In all cases where type IIA curves were obtained, the Arrhenius parameters derived from the α- and the β- parts of the curves were closely similar, and only the α-values are therefore quoted. Other quantities are as defined in Part III. Pre-exponential factorsf or both supported and unsupported catalysts are expressed as (g. of metal)$^{-1}$, and as m.$^{-2}$ where the surface area is known. Hydrogen was admitted first to the reaction vessel unless otherwise stated, and rate constants were evaluated from series of experiments in which the hydrogen pressure was varied through at least 200 mm. within the range 30—360 mm.

Table 1. *Results for iron, cobalt, and copper catalysts.*

Catalyst	Fe–p	Fe–I	Fe–II	Co–p	Co–I	Cu–p	Cu–p	Cu–p	Cu–I
$P_{C_2H_2}$ *	30	30	30	30	30	17	32	62	30
Metal (g.)	0·20	0·30	0·31	0·20	0·24	0·20	0·20	0·20	0·25
Temp. range	145—225°	108—162°	208—254°	107—157°	111—156°	150—195°	150—195°	150—195°	121—175°
E_A †	7·1	8·7	15·1	4·1	9·0	19·2	16·9	21·0	21·0
E_B †	—	—	—	—	—	5·0	5·0	—	3·2
ΔE_B †	—	—	—	—	—	−14·6	−13·3	—	−17·8
$\log_{10} A_A$ ‡	1·76	2·62	4·63	1·30	3·66	8·26	7·21	7·75	9·63
$\log_{10} A_B$ ‡	—	—	—	—	—	1·06	1·09	—	1·80
$\log_{10} \Delta A_B$ ‡	—	—	—	—	—	−6·38	−7·26	—	−9·72
Surface area §	—	4·68	—	—	1·44	—	—	—	1·01
$\log_{10} A_A$ ‖	—	1·95	—	—	3·50	—	—	—	9·63
$\log_{10} A_B$ ‖	—	—	—	—	—	—	—	—	1·80

* Initial pressure (mm.). † kcal. mole^{-1}. ‡ min.$^{-1}$ (g. of metal)$^{-1}$. § m.^{2} g.$^{-1}$. ‖ min.$^{-1}$ m.$^{-2}$.

Iron, Cobalt, and Copper Catalysts.—The principal results are shown in Table 1. With iron and cobalt catalysts, type IIA curves were obtained irrespective of the hydrogen : acetylene ratio and of the order of admission of reactants: there was no indication of an inflexion in the

[5] Best and Russell, *J. Amer. Chem. Soc.*, 1954, **76**, 838; see also Hall and Alexander, *J. Phys. Chem.*, 1957, **61**, 1564.

XUM

rate *versus* hydrogen pressure plots up to at least 300 mm. of hydrogen, and the results are therefore fully described by the rate expression

$$-\mathrm{d}p/\mathrm{d}t = k_A P_{H_2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

When hydrogen was admitted first to the cobalt–pumice catalyst, $-\Delta p_\alpha$ increased quite markedly with hydrogen pressure for hydrogen : acetylene ratios less than about three, but for higher ratios it remained constant at about two-thirds of the initial acetylene pressure. It was however independent of hydrogen pressure when acetylene was added first.

Of the iron powders, that (Fe–I) prepared by reduction of the oxide *in situ* was active in a much lower temperature range than that (Fe–II) reduced in an external system; the same was found for nickel,[1] and the same explanation may apply. With cobalt–pumice, an activation energy of 4·3 kcal. mole^{-1} and a value of $\log_{10} A_A$ of 1·20 min.$^{-1}$ g.$^{-1}$ were obtained when acetylene was admitted first.

Copper-pumice as catalyst. At and below 167° the dependence of rate on hydrogen pressure was of the form

$$-\mathrm{d}p/\mathrm{d}t = R_D + k_A P_{H_2} + k_B(P_{H_2} - P_{H_2}^0) \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

when the initial acetylene pressure was not greater than 32 mm.; above 167° the third term of the rate expression was not detectable because of the rapid way in which k_B/k_A fell with rising temperature (see Table 1 for values of ΔE_B). Table 2 gives values of the parameters in equation

TABLE 2. *Dependence of parameters in equation* (3) *on temperature and acetylene pressure.*

Temp.	$P_{C_2H_2}$ (mm.)	R_D (mm. min.$^{-1}$)	$P_{H_2}^0$ (mm.^{2})	$10^2 k_A$ (min.$^{-1}$)	$10^2 k_B$ (min.$^{-1}$)
150·0°	17	0·38	102	0·38	0·48
,,	32	0·44	147	0·66	0·46
,,	62	0·46	212	1·06	—
167·5	17	0·50	75	0·86	0·60
,,	32	0·55	90	1·25	0·55
,,	62	1·05	200	1·70	—

(3) at 150° and 167·5°; failure to observe the " two-rate " effect with 62 mm. of acetylene at either of these temperatures was presumably due to the use of insufficiently high hydrogen pressures. It has been supposed that the R_D term represents a catalytic decomposition or polymerisation which for a fixed acetylene pressure and temperature proceeds at a rate independent of the hydrogen pressure. From Table 2, together with results obtained at 182·5 and 195° values of E_A, E_B, etc. have been calculated (see Table 1): E_A has a mean value of 19·0 ± 1·4 kcal. mole^{-1} which is probably independent of acetylene pressure. That the processes whose rate constants are k_A and k_B are hydrogenations substantially free from decomposition or polymerisation is shown by the very satisfactory nature of the Arrhenius plots. Values of E_D show no regular trend with changing acetylene pressure, and lie between 22·5 and 25·0 kcal. mole^{-1}.

Consideration of the results in Table 2 and of other measurements at higher temperatures shows that at every temperature both R_D and k_A depend on a fractional positive power x of the acetylene pressure; values of x (which are uncertain by ±0·05) are as follows.

Positive orders in acetylene were also found for certain nickel catalysts.[1] The increase in

Temp.	150°	167·5°	182·5°	195°
x for k_A dependence	0·28	0·26	0·53	0·80
x for R_D dependence	0·17	0·52	0·72	0·77

order in acetylene for k_A with increasing temperature denotes desorption of the acetylene, and the " two-rate " effect only seems to appear when the adsorption of acetylene is fairly strong. k_B is almost independent of acetylene pressure at 150° and 167°.

Copper powder as catalyst. Similar results were obtained; the " two-rate " effect was observed at 121° and 135° (but not at higher temperatures), $P_{H_2}^0$ being respectively 95 and 78 mm. A decomposition was again found, and R_D appeared to increase linearly from 0·3 to 0·9 mm. min.$^{-1}$ between 121° and 175°.

A very satisfactory " compensation effect " exists between all the activation energies and log A terms quoted thus far: the equation is $\log_{10} A_i = 0{\cdot}55E_i - 1{\cdot}5$.

The corresponding equation for nickel catalysts [1] was $\log_{10} A_i = 0{\cdot}48E_i + 0{\cdot}40$.

Nickel–Copper and Nickel–Cobalt Alloys.—Physical characteristics. Table 3 gives the observed lattice parameters (a_0) in Å and the compositions to which these values correspond, obtained by comparison with Coles's results [6] for the nickel–copper system and with Taylor's [7] for the nickel–cobalt system: surface areas are also quoted. The accuracy of the lattice parameter measurements varied because of the variable degree of crystallinity of the powders. All

TABLE 3. *Lattice parameters, composition, and surface areas of alloys.*

	Nickel–copper				
Copper, nominal (%)	0	20	40	60	80
Lattice parameter (Å)	3·5235 ± 0·0005	3·5405 ± 0·0005	3·555 ± 0·001	3·567 ± 0·001	3·5910 ± 0·0005
Copper observed (%)	0	21·0 ± 0·5	39·0 ± 1·0	52·5 ± 1·0	79·0 ± 0·5
Surface area ($m.^2 g.^{-1}$)	0·41	0·79	0·76	0·54	0·49

	Nickel–cobalt			
Cobalt, nominal (%)	20	40	60	80
Lattice parameter (Å)	3·526 ± 0·001	3·531 ± 0·001	3·5355 ± 0·001	3·5395 ± 0·001
Cobalt observed (%)	17 ± 5	36 ± 5	58 ± 5	77 ± 5
Surface area ($m.^2 g.^{-1}$)	0·52	1·28	0·98	1·30

the nickel–cobalt alloys had the face-centred cubic structure; pure cobalt was also examined and found to be mainly in this form, although a little of the theoretically more stable close-packed hexagonal form was also present. No alloy contained detectable free metal (<2%). The only alloy not showing the expected composition within the accuracy of the measurements was that designed to contain 60% of copper and 40% of nickel. Hall and Alexander [7a] have recently investigated by *X*-ray spectroscopy nickel–copper alloys prepared by the method used here, but reduced at only 350°, and have concluded from the degree of line-broadening that inhomogeneity within a crystallite in no case exceeds 3%. Surface areas of copper and cobalt powders are in Table 1.

Kinetic characteristics. Series of experiments were performed with about 0·25 g. of each alloy; the rate expression (1) applied throughout, and in each case the parameters of this expression were determined in the usual manner at five temperatures covering a range of 20—40°. The principal results are shown in Table 4. Pressure–time curves were generally of

TABLE 4. *Kinetic characteristics of nickel alloy catalysts.*

	Nickel–copper						Nickel–cobalt			
Nickel * ...	100	80	60	40	40	20	80	60	40	20
Temp. range	73—150°	71—110°	83—110°	92—119°	99—122°	123—148°	114—137°	105—124°	74—108°	123—165°
E_A †	8·2	15·1	20·1	21·3	20·2	25·2	19·2	21·0	12·5	16·0
E_B †	15·1	16·4	17·1	8·9	7·8	18·2	13·7	18·2	12·0	6·2
ΔE_B †	7·3	1·7	−3·0	−13·2	−12·8	−7·1	−5·5	−2·5	−1·0	−10·8
$\log_{10} A_A$ ‡ ...	5·0	8·1	11·0	11·4	10·6	12·5	9·6	10·8	6·4	7·3
$\log_{10} A_B$ ‡ ...	8·3	9·6	9·2	4·2	3·4	8·8	6·6	9·5	5·6	1·7
$\log_{10} \Delta A_B$ ‡	4·3	1·0	−1·7	−7·6	−7·1	−3·9	−3·0	−1·3	−1·6	−6·0
$\log_{10} A_A$ ‖ ...	5·4	8·2	11·1	11·8	—	12·8	9·8	10·7	6·5	7·2
$\log_{10} A_B$ ‖ ...	8·7	9·7	9·3	4·6	—	9·1	6·8	9·4	5·7	1·6

The results for nickel are taken from Part III; those for copper and cobalt are to be found in Table 1.

The surface area of the catalyst used in the repeat measurement (col. 5) was not determined: in estimating the activities for Fig. 1, the area has been assumed to be 0·76 $m.^2 g.^{-1}$.

* Nominal percentage. †‡‖ See Table 1.

type I above $P_{H_2}^0$ and of type III below it; no decomposition of acetylene (*i.e.*, no R_D term) was ever detected. Two samples of nickel–copper alloy containing nominally 40% of nickel were prepared from mixed oxides drawn from the same batch, to check the reproducibility of measurements. Values of $P_{H_2}^0$ tended to fall with decreasing temperature, but generally very irregularly, and there was evidence that other variables (*e.g.*, the age of the catalyst) were operative. $P_{H_2}^0$ values lay between 70 and 175 mm. for nickel–copper alloys and between 70 and 190 mm. for nickel–cobalt alloys. The initial acetylene pressure was 30 mm. in all cases.

In both series, changes in activation energies and in the corresponding specific log *A* terms

[6] Coles, *J. Inst. Metals*, 1956, **84**, 346.

[7] Taylor, *ibid.*, 1950, **77**, 585.

[7a] Hall and Alexander, *J. Phys. Chem.*, 1957, **61**, 242.

XUM

run parallel in a striking manner. " Compensation effects " therefore result, log A_i being simply proportional to E_i; the proportionality constants are 0·56 in the nickel–copper series and 0·50 in the nickel–cobalt series. The value for nickel catalysts was 0·48 and for the other pure metals 0·55; the differences between all these values are within experimental error.

With increasing copper content, E_A rises from 8 to 25 kcal. mole^{-1} at 80% of copper, and thereafter falls slightly; E_B and ΔE_B respectively rise slightly and fall but at above 60% of copper they behave irregularly. Experiments with a second sample of 60% copper alloy showed that activation energies (and particularly ΔE_B) were quite closely reproducible, so that the apparently irregular behaviour is probably not adventitious. With increasing cobalt content, E_A at first rises steeply, reaching a maximum at 40% of cobalt, but thereafter it changes erratically; neither E_B nor ΔE_B changes smoothly with composition.

The occurrence of compensation effects obscures possible effects of composition on activity except insofar as this is revealed by the temperature range for satisfactory operation. From the results in Tables 1 and 4, values of k_A and k_B have been computed for all catalysts at characteristic temperatures of 50°, 100°, 150°, and 200°, and in Fig. 1 these values are plotted against composition. The availability of results covering a continuous series of solid solutions from cobalt through nickel to copper provides a broad basis for considering how the electronic factor operates in the hydrogenation of acetylene.

Discussion

The " Two-Rate " Effect.—The " two-rate " effect has not been found with any type of iron or cobalt catalyst under conditions where it appears with nickel and copper catalysts, although in the nickel–cobalt alloy series the effect persists through to the alloy containing only 20% of nickel. We conclude provisionally that the mechanism suggested [4] for the reaction over nickel below $P_{H_2}^0$ holds over a much wider range of conditions with iron and cobalt. The second mechanism is believed [8] to be caused by molecular hydrogen's initiating a kinetically independent mechanism, and we now attempt an interpretation of the results on this model.

Although the rate of the second process always increases with temperature, its activation energy E_B varies widely; it is high for nickel (15 kcal. mole^{-1}), low for copper (3 kcal. mole^{-1}), and presumably zero for iron and cobalt. In the alloy series, values of E_B lie in the range 16 ± 2 kcal. mole^{-1} from 40% of cobalt to 80% of copper inclusive, apart from the unexplained (but reproducible) low values for the 60% copper alloy. If the true activation energy of the second process were constant until at least the *d*-band is filled, the rapid fall in E_B at the cobalt-rich end of the nickel–cobalt series would reflect an increase in the heat of adsorption of molecular hydrogen, and we may expect that there will be a maximum permissible value for this quantity which if exceeded would cause a spontaneous transition of adsorbed hydrogen from the molecular to the atomic form. However this type of explanation can scarcely be applied to interpret the behaviour of copper for whose low E_B value there is no immediate explanation. A second type of hydrogen chemisorption which may be molecular in form has been observed on nickel films [9] but not on copper films [10] at room temperature; molecularly adsorbed hydrogen is probably only stable on iron catalysts at low temperatures.[11] We conclude that the present results accord reasonably with what might be expected on the basis of the previously proposed mechanism.

Relative Activities of the Pure Metals.—Changes in the constitution of the catalyst for a chosen reaction may affect its activation energy, its pre-exponential factor, or both simultaneously: experimental investigation of these relations gives information on the effect of the parameters of the catalyst on the energetics of the reaction path, and on the basic activity of the unit catalytic site. In the present case, E_A has a low and approximately constant value for iron, cobalt, and nickel powders ($8{\cdot}6 \pm 0{\cdot}4$ kcal. mole^{-1}) so that

[8] Bond, *J.*, 1958, 4288 (Part II).
[9] Mignolet, *Rec. Trav. chim.*, 1955, **74**, 701; Sachtler, *Bull. Soc. chim. belges*, 1958, **67**, 369.
[10] Bloyaert, D'Or, and Mignolet, *J. Chim. phys.*, 1957, **54**, 53.
[11] Kummer and Emmett, *J. Phys. Chem.*, 1952, **56**, 258.

activity differences between these three metals reside chiefly in log A: for copper powder, E_A is 21 kcal. mole^{-1}, but log A is not large enough to compensate, and copper therefore has the lowest activity of the pure metals. The same is also true of the supported metals, although here E_A for the *d*-metals covers a wider range (*ca.* 4—10 kcal. mole^{-1}); E_A for copper is high (*ca.* 19 kcal. mole^{-1}), and copper is again the least active metal. The agreement between the Arrhenius parameters for supported and unsupported metals is satisfactory for iron and copper but poor for cobalt. The less active iron powder (Fe–II) has a much higher activation energy than the more active one (Fe–I).

Of more practical interest is the comparison of the activities of the metals at a chosen temperature: Table 5 gives the values of k_A and of k_B (both $\times 10^2$) at 100° for supported and unsupported metals. The activity *order* based on k_A is in both cases Ni > Co > Fe > Cu, but for k_B Ni > Cu. It is significant that the actual values of k_A and k_B per g. of metal differ by no more than a factor of three except in the case of k_B for copper: the absolute activities of the metals per unit weight are therefore generally about the same regardless of whether they are supported on pumice or not. Correction to unit surface area (line 3 of Table 5) does not change the activity order, but increases the disparity between the most and least active metals.

TABLE 5. *Values of k_A and k_B at* 100°.

	k_A				k_B	
	Fe	Co	Ni	Cu	Ni	Cu
10^2k (min.$^{-1}$ g.$^{-1}$) for supported metals ...	0·40	3·4	47	0·21	21	1·1
10^2k (min.$^{-1}$ g.$^{-1}$) for unsupported metals	1·3	2·8	24	0·18	28	8·4
10^2k (min.$^{-1}$ m.$^{-2}$) for unsupported metals	0·28	1·9	60	0·18	66	8·3

While the relative activities of the *d*-metal powders is approximately independent of temperature, the activity of copper relative to that of these metals increases with rising temperature because of its higher activation energy, and at some high temperature copper will for this reason be more active than the other metals.

It now remains to decide with what parameter of the *d*-metals we may seek to correlate their differences in activity. It is fruitless to relate them to variations in metallic radius or percentage of *d*-bond character, both of which are essentially the same for all three metals. However log A decreases smoothly as the concentration of *d*-band holes [h_d] (as given either by saturation moments or by direct measurement [12]) increases, and we conclude that for the hydrogenation of acetylene the electronic constitution of the metal determines its activity through its influence on the pre-exponential term rather than on the activation energy. Iron and nickel films are about equally effective for hydrogenating ethylene,[13] while for the conversion of styrene into ethylbenzene a supported iron catalyst is much less active than supported nickel.[14]

Relative Activities in the Alloy Series.—The foregoing considerations point the direction in which the results for the alloy series are to be interpreted, but rather more detailed interpretation is made possible by the finding that the activity patterns are markedly temperature-dependent (see Fig. 1). The results for the pure metals were adequately discussed in terms of the changing concentration of *d*-band holes, but theoretical considerations have shown [15] that it is not only the energy of the Fermi surface but also the density of the electron levels $n(E)$ at this point which determines catalytic activity.

It is convenient now to consider separately our results for the two alloy series.

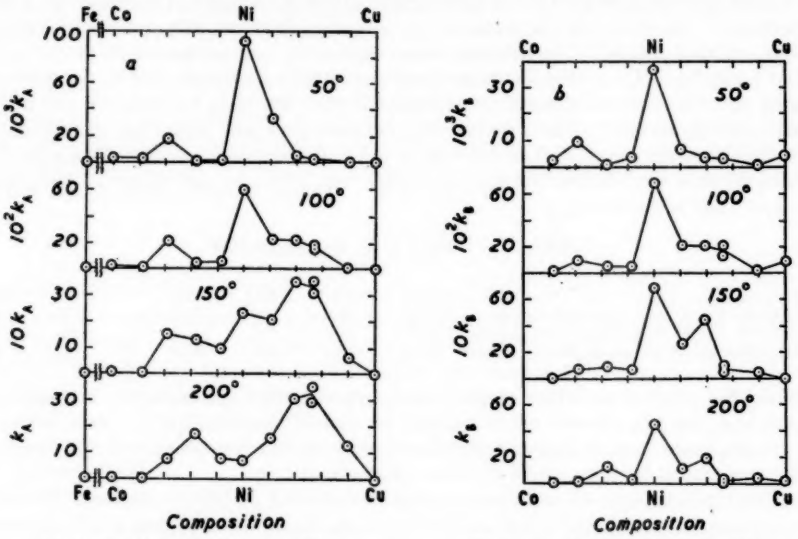
Nickel–Copper Alloys.—As the concentration of copper is increased, the number of *d*-band holes per atom decreases linearly and is presumed to become zero at about 60% of copper; through this range of composition the density of electron levels $n(E)$ remains almost constant, falling rapidly only when the percentage of copper exceeds 60%.[14] Coles

[12] Weiss and de Marco, *Rev. Mod. Phys.*, 1958, **30**, 59.
[13] Kemball, *J.*, 1956, 735.
[14] Dowden and Reynolds, *Discuss. Faraday Soc.*, 1950, **8**, 184.
[15] Dowden, *J.*, 1950, 242.

XUM

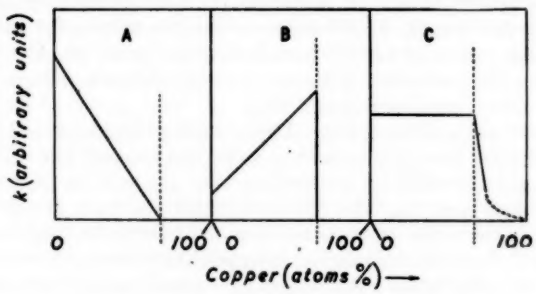
has however recently pointed out the substantial differences between the nickel–copper and the palladium–silver system, and has suggested that *d*-band holes still exist in the copper-rich end of the nickel–copper system;[16] a recent determination of the number of *d*-electrons in copper gives $9{\cdot}8 \pm 0{\cdot}3$.[12] The existence of a small concentration of *d*-band holes in copper, but not in silver or gold, would interpret the large differences between these metals in a wide variety of catalytic reactions.

FIG. 1. *Activity patterns for nickel–copper and nickel–cobalt alloys at various temperatures.*



(*a*) k_A as a function of composition. (*b*) k_B as a function of composition.

FIG. 2. *Idealized possible forms for the dependence of activity on composition for nickel–copper alloys.*



We may visualize three possible forms of activity patterns, represented in an idealized manner in Fig. 2. In case A, there is a progressive *decrease* in activity as $[h_d]$ falls until it becomes zero at about 60% of copper; hydrogenation of styrene on nickel–copper alloys[14] conforms to this pattern. In case B, the activity *increases* progressively as $[h_d]$ falls until a sudden decrease marks the filling of the *d*-band; this is the pattern expected if there is a continuous decrease in strengths of adsorption as the *d*-band is filled, and Best and Russell's[5]

[16] Coles, *Proc. Phys. Soc.*, 1952, **65**, *B*, 221.

results on the hydrogenation of ethylene on nickel–copper powders suggest this pattern. Case C shows the effect expected if $n(E)$ determines the activity or if the activity is independent of $[h_d]$ as long as $[h_d] > 0$: Rienäcker and Bommer's results [17] for the hydrogenation of ethylene on nickel–copper foils at 500° conform approximately to this pattern.

We have found that E_A increases sharply with increasing copper content (Table 1) but is almost constant (20—25 kcal. mole^{-1}) between 40 and 100% of copper: there is therefore no sign of any marked change in E_A where the *d*-band is filled. However the low values of E_B at 60% of copper may be caused by an effect of *d*-band filling. Owing to the operation of a partial compensation effect, it is more instructive to discuss activity patterns (Fig. 1) than log A terms. At 100° both k_A and k_B are about constant over the range 20—60% of copper (respectively 18—20 $\times$ 10^{-2} and 20—21 $\times$ 10^{-2} min.$^{-1}$ m.$^{-2}$), values for nickel being each about three times greater; between 60 and 80% of copper both values fall tenfold, and there is a further fall between 80 and 100% of copper. There is thus a substantial fall in activity near the point where the *d*-band is presumably filled, probably caused by the change in the gradient of $n(E)$. The patterns are therefore intermediate between cases A and C. We can now describe the effect of temperature on the activity patterns in terms of our three idealized cases. At 50°, the patterns are still intermediate between cases A and C, but the contribution of A has increased; for k_A it is intermediate between B and C at 150° and predominantly represented by B at 200°. For k_B at these temperatures the pattern is complex and presumably is composed of elements of each of the three cases.

The agreement (especially at low temperatures) between the activity patterns based on k_A and k_B is significant. It implies that the electronic factor manifests itself equally in both mechanisms, perhaps through the energy required to break a carbon–metal bond in converting chemisorbed acetylene into an adsorbed vinyl radical.

We summarise our conclusions with reference to activity patterns based on k_A by the following generalisations: at low temperatures, the activity decreases with decreasing $[h_d]$; at intermediate temperatures, it is independent of $[h_d]$ or is determined by $n(E)$; at high temperatures, it increases with decreasing $[h_d]$ in the expected manner.

Nickel–cobalt alloys. There is again agreement between the activity patterns based on k_A and k_B (Fig. 1). If we accept the view that the low-temperature activity pattern for nickel–copper is determined by $[h_d]$, then activity in the nickel–cobalt series should increase with cobalt content. But this is not so: hence the fall in activity with increasing cobalt content must be ascribed to a falling value of $n(E)$.[14] However at high temperatures there is a reasonably smooth increase of activity with falling $[h_d]$, in agreement with the results for the nickel–copper series. The activity maximum at 60% of cobalt appears to be genuine, but no acceptable explanation has yet been found for it: it is probably only coincidental that it occurs near the composition (*ca.* 54% of cobalt) where there is exactly one *d*-band hole per atom. The maximum becomes progressively less marked with rising temperature.

With increasing cobalt content, E_A at first rises steeply and subsequently falls more slowly (Table 1). This is not easy to understand, since no electronic parameter shows a maximum between nickel and cobalt: it may simply be that the activation energy is affected by the inhomogeneity of the catalyst, just as the electrical resistance of alloys is always greater than that of its constituents.

We thank Mr. D. A. Dowden of Imperial Chemical Industries Limited, Billingham Division, for arranging the determination of the surface areas and the *X*-ray spectroscopy of the catalysts. We thank this University for a maintenance grant (to R. S. M.).

THE UNIVERSITY, HULL. [*Received, March 18th,* 1959.]

[17] Rienäcker and Bommer, *Z. anorg. Chem.*, 1939, **242**, 302.

716. *Substituent Effects in Fluorene Derivatives. Part I. The Reaction of Substituted 9-Bromofluorenes with Potassium Iodide in Acetone.*

By J. D. Dickinson and C. Eaborn.

The rates of reaction of some substituted 9-bromofluorenes with potassium iodide in acetone have been measured. Except possibly for the methoxy-group, 2-substituents exert influences consistent with their being regarded as analogous to *meta*-substituents in reactions of benzyl halides.

Effects of nuclear substituents on reactions at the 9-position of fluorene are of special interest because polar influences may be transmitted to this position both directly through the substituted ring and indirectly through the other ring. For example, a group in the 2-position can most simply be regarded as equivalent to a *meta*-substituent in benzyl compounds, but transmission of tautomeric effects through the second ring, as in (I), could give the group some of the characteristics of a *para*-substituent also. (The coplanarity of the nuclei [1] favours conjugation between the rings.) Such conjugation, involving the $+T$ effect of the 2-methoxy-group, appears to operate in the rearrangement of 9-fluorenyl azides to give phenanthridines [2] (an electrophilic reaction in which the high electron demand will call forth the $+E$ effect very strongly, as in acid-catalysed decomposition of 1,1-diphenylethyl azides [3,4]), and it is likely that transmission of a $-T$ effect of the 2-nitro-group to the 7-position is responsible for the formation of 2,5-dinitrofluorene along with the 2,7-compound in nitration of 2-nitrofluorene.[5] As a first step in a progressive study of substituent effects in the fluorene system we have measured the rates of reaction of some substituted 9-bromofluorenes with potassium iodide in acetone, a reaction of the S_N2 type.

Sampey and King [6] examined the reaction of 9-bromofluorene with potassium iodide in acetone and found that formation of iodine prevented use of the usual " iodine cyanide " method for determination of iodide ion in presence of bromide ion. They attributed the iodine formation to reaction (1) (R = 9-fluorenyl).

$$2RI \longrightarrow 2RR + I_2 \quad \ldots\ldots\ldots\ldots (1)$$

We have found that iodine is not formed in a solution of 9-iodofluorene in acetone in the dark unless iodide ion is present. The iodine formation presumably involves abstraction of positive iodine from the 9-iodofluorene, as in reaction (2). [An analogous reaction occurs between tri-(*p*-nitrophenyl)methyl bromide and iodide ion [7].]

$$RI + I^- \longrightarrow R^- + I_2 \quad \ldots\ldots\ldots\ldots (2)$$

The fluorenyl anion, which may never be completely free, could disappear by several reactions, one of which might be that shown in reaction (3).

$$R^- + RI \longrightarrow RR + I^- \quad \ldots\ldots\ldots\ldots (3)$$

A reaction of type (2) would not be expected to occur readily with 9-bromofluorene, and this halide with iodide ion does not give iodine except after such a time that significant amounts of iodofluorene must be present. It seems safe to assume that the reactions

[1] Brown and Bortner, *Acta Cryst.*, 1954, **7**, 139.
[2] Arcus and Coombs, *J.*, 1954, 4139.
[3] Ege and Sherk, *J. Amer. Chem. Soc.*, 1953, **75**, 354.
[4] Okamoto and Brown, *J. Org. Chem.*, 1957, **22**, 485; Brown and Okamoto, *J. Amer. Chem. Soc.*, 1958, **80**, 4979.
[5] Anantakrishnan and Hughes, *J.*, 1935, 1607.
[6] Sampey and King, *Bull. Furman Univ., Furman Studies*, 1949, **31**, No. 5, p. 22.
[7] Hawthorne, *J. Amer. Chem. Soc.*, 1955, **77**, 5739; Kosower, *ibid.*, 1958, **80**, 3267.

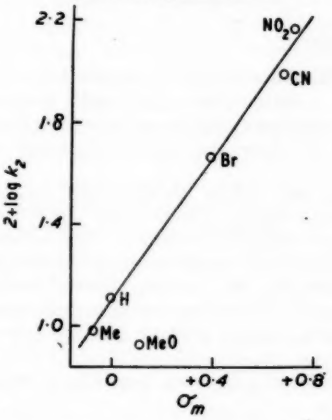
giving rise to iodine do not interfere directly with the interaction of 9-bromofluorene and iodide ion.

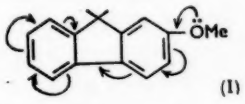
Iodine formation does not interfere with the analysis provided a low concentration of 9-bromofluorene is taken, for at low concentrations iodine is taken up by acetone,[8] and the

$$RI + I^- + COMe_2 \longrightarrow I{\cdot}CH_2{\cdot}COMe + R^- + H^+ + I^- \quad . \quad . \quad . \quad . \quad . \quad (4)$$

overall result is as in reaction (4), the iodide-ion concentration being unchanged by the sequence of reactions. The possibility of disturbance of the kinetics by interactions of the fluorenyl anion or other intermediates with the 9-bromofluorene is ruled out by the fact that good second-rate constants are obtained during the first 60% of reaction provided excess of 9-bromofluorene is taken to force the exchange towards completion.

Plot of $\log k_2$ *for 2-substituted 9-bromofluorenes against* σ_m.





(I)

The observed rate constants, k_2, are shown in the Table along with the apparent activation energies, E. Since only two temperatures, 10° apart, were used, values of E are subject to a large error, and we cannot even be certain that the opposition of the trends in rates and activation energies is real.

Reaction of 9-*bromofluorenes*, $X{\cdot}C_9H_8Br$, *with potassium iodide in acetone.*

X	2-NO_2	2-CN	2-Br	3-Me	2-H	2-Me	2-MeO
$10k_2$ (at −0·04°) [a]	14·9	9·8	4·56	1·20	1·27	0·98	0·85
$10k_2$ (at −10·25°) [a]	3·68	2·18	1·17	0·332	0·320	0·311	0·271
E (kcal./mole)	19·6	21·1	19·0	18·0	19·3	16·1	16·0

[a] Min.$^{-1}$ mole^{-1} l.

The reaction is facilitated by strongly electron-withdrawing substituents. When $\log k_2$ (at −0·04°) for the 2-substituted compounds is plotted against the substituent constants, σ_m,[9] applicable to the corresponding *meta*-substituents in benzene derivatives (see Figure), the points fall satisfactorily on a straight line except that for the 2-methoxy-group, which lies off the line in the direction expected if it supplied electrons by the mechanism shown in (I).* Unfortunately, in the absence of experimental evidence we cannot be

[8] Dawson and Leslie, *J.*, 1909, **95**, 1860.
[9] Jaffé, *Chem. Rev.*, 1953, **53**, 191.

* It would not be surprising to find only the 2-methoxy-group showing such effects. If a 2-substituent is regarded as partly *para* in character, this will make little difference, with, for example, the nitro-group, which in spite of its strong $-T$ effect has similar values of σ_m and σ_p (0·710 and 0·778, respectively).[9] For the methoxy-group, $\sigma_m = +0{\cdot}115$, and $\sigma_p = -0{\cdot}268$.

sure that the *m*-methoxy-group has a " normal " effect in the corresponding reactions of benzyl halides. For the reaction between benzyl chlorides and iodide ion in acetone at 0·1,[10] we find that the log k_2–σ plot approximates to a straight line for the *m*-Cl, *m*-Br, *m*-I, and *m*-NO_2 substituents but the point for the *m*-F and all the points for *para*-groups are well away from the line. Further, the effects of substituents in the benzyl chloride reaction are complex, because, while the electron-withdrawing halogen and nitro-groups facilitate reaction,[10] so also does the *p*-Me group,[11] and this an example of the type of reaction previously discussed,[12] in which use of simple σ-constants is unsatisfactory. It is interesting that a 3-Me substituent in the fluorene series appears to activate at −10·25° (at −0·04° the rate is not significantly different from that of the unsubstituted compound), which is consistent with regarding it as analogous to a *para*-substituent in benzyl halides.

We must conclude that the data in the Table do not conflict with the simplest assumption that in this reaction 2-substituents are analogous to *meta*-substituents in benzyl compounds.

Experimental

The preparation and properties of the 9-bromofluorenes have been described.[13]

Potassium iodide was dried at 100° for 2 hr. Acetone was boiled with potassium permanganate, fractionated, dried under reflux with anhydrous calcium sulphate, and fractionated from fresh calcium sulphate. One stock, protected from atmospheric moisture, was used throughout.

Equal volumes of acetone solutions of potassium iodide (0·01M) and bromofluorene (0·04M) were mixed at the thermostat temperature (−0·04° or −10·25°, both ±0·05°). Aliquot parts (10 ml.) were withdrawn at suitable times, and added to ice-water. The iodide-ion concentration was determined by Dostrovsky and Hughes's modification of the Lang cyanide method,[14] titrations being carried out under standard illumination from a 100 w daylight lamp. With 8—10 samples withdrawn during the first 60% of reaction, the mean deviation of the individual rate constants from their average was <5% (usually <3%). Average rate constants could be duplicated to within 3%.

The following typical run refers to 9-bromo-3-methylfluorene (initially 0·0178M), with potassium iodide (initially 0·00504M) at −0·04°.

Time (min.)	0	87·3	140·5	203·6	260·3	292·3	332·5	361·6	411·3	492·3
Titre (ml.)	25·2	21·2	18·8	17·2	15·2	13·9	12·5	12·4	11·5	9·3
10^3k_2	—	114	122	111	117	123	129	120	118	128

No iodine was formed in a solution of 9-iodofluorene (1 g.) in acetone (100 ml.) during 3 days at room temperature (protected from light and air) or during 50 hours' refluxing (protected from light). With exposure to sunlight, 9% of possible iodine was liberated in 10 hours' refluxing. In the dark, similar solutions containing also 1 g. of sodium iodide gave 65% of possible iodine in 30 hr. at room temperature and 84% in 4 hours' refluxing.

The University, Leicester. [*Received, April 10th*, 1959.]

[10] Bennett and Jones, *J.*, 1935, 1815.
[11] Charlton and Hughes, *J.*, 1956, 855.
[12] Swain and Langsdorff, *J. Amer. Chem. Soc.*, 1951, **72**, 2813; Bartlett in Gilman's " Organic Chemistry," Wiley and Sons, New York, Vol. III, 1953, pp. 33—35; Dickinson and Eaborn, *J.*, 1959, 3036.
[13] Dickinson and Eaborn, *J.*, 1959, 2337.
[14] Dostrovsky and Hughes, *J.*, 1946, 161.

717. *Submicro-methods for the Analysis of Organic Compounds. Part X.* Determination of Fluorine.*

By R. Belcher, M. A. Leonard, and T. S. West.

Fluorine is determined in organic compounds on the submicro-scale by combustion in an oxygen-filled flask. The fluoride ion is then determined by a new reaction. Cerium(III) alizarin complexone forms a blue complex with fluoride ion which can be measured spectrophotometrically. There is no interference from other halides, sulphate, or nitrate. Phosphate or arsenate in amounts equivalent to fluoride has little effect.

The accuracy of the results is equivalent to that of the micro-procedure.

The determination of fluorine provides difficulties on any scale. The two most widely used methods, precipitation as lead chlorofluoride and titration with thorium nitrate, are not suitable for application on the submicro-scale. The solubility of lead chlorofluoride is too great and in any case only the titrimetric procedure, which is less satisfactory than the gravimetric procedure, could be applied; although the thorium nitrate titration is very sensitive, it is necessary to make control titrations on aliquot portions of the solution to establish the electrolyte concentration;[1] this is inconvenient on the submicro-scale. Attempts were made to precipitate calcium fluoride quantitatively so that a final complexometric titration could be made, but even in the presence of organic solvents, precipitation was incomplete in the minimum volume of solution which could be used.[2] Spectrophotometric methods were considered, but those which existed depend on the bleaching effect of fluoride ion on a suitably coloured metal complex and are subject to interference by anions which could be present after mineralisation of an organic compound.

Fortunately, studies in another field revealed a new reaction of the fluoride ion. Alizarin complexone (1,2-dihydroxyanthraquinon-3-ylmethylamine-*NN*-diacetic acid)[3] forms a red chelate with cerium(III); in the presence of fluoride ion, a new blue complex is formed,[4] whose nature is being investigated. As far as we know, this is the first known positive colour reaction of the fluoride ion. It is very sensitive and, unlike the common bleaching reactions, unaffected by sulphate ions. Other halides do not interfere, nor do phosphate and arsenate ions in moderate amounts. Hence this reaction appears ideal for the determination of fluorine in organic compounds, for the usually associated elements form anions which have little or no influence on it.

Within the range 15—50 μg. an absolute accuracy of ±0·5% can be achieved.

In qualitative tests, phosphate did not interfere unless amounts six-fold those of the fluoride ion were present. Only two compounds containing both phosphorus and fluoride were available; the results were as satisfactory as with the other compounds examined (Table 1).

Decomposition of the Sample.—Although there appears no reason why the conventional sodium fusion method could not be applied, the "oxygen-flask" method, first used by Hempel[5] in 1892 and revived in recent years by Mikl and Pech[6] and Schöniger,[7] was tried because of its speed and simplicity. Excellent results were obtained.

The sample is wrapped in filter-paper and clamped in a platinum wire attached to the stopper of a 250 ml. conical flask. Water is placed in the flask to absorb acid gases and the flask is filled with oxygen. The paper is lighted and the stopper immediately replaced.

* Part IX, *J.*, 1959, 2882.

[1] Belcher, Caldas, Clark, and Macdonald, *Mikrochim. Acta*, 1953, 283.
[2] Bhasin, unpublished work.
[3] Belcher, Leonard, and West, *J.*, 1958, 2390.
[4] *Idem*, *Talanta*, 1959, **2**, 92.
[5] Hempel, *Z. angew. Chem.*, 1892, **5**, 393; cf. Macdonald, *Ind. Chemist*, 1959, **35**, 33.
[6] Mikl and Pech, *Chem. Listy*, 1952, **46**, 382.
[7] Schöniger, *Mikrochim. Acta*, 1955, 123.

XUM

Combustion is complete in a few seconds. When absorption of acid gases is complete the fluoride ion is determined spectrophotometrically as the blue complex of cerium(III) alizarin complexone.

Some compounds which contained $-CF_3$ gave low results. This has been noted previously by other investigators who have used the " oxygen-flask " method on the micro-scale [8] and was attributed to formation of carbon tetrafluoride; when they mixed the sample with sodium peroxide, effective decomposition was obtained. This was tried in the present instance, but the results were little better. However, when potassium chlorate was used the combustion proceeded satisfactorily.

A disadvantage of this method is that the paper can only be reduced to a certain size to allow convenient handling. This restricts reduction of the volume of the flask; it is essential that enough oxygen be present to ensure complete combustion of the paper and compound. A 250-ml. flask was the minimum size which could be used and the subsequent rinsing so diluted the solution that it was necessary to take about twice as much sample as is usual on the submicro-scale (100 μg). When this problem has been solved it should be possible to use 50 μg. or even smaller sample weights. The sodium fusion method would not have these limitations, but is far less convenient. More refined methods of spectrophotometry should also repay investigation.

Selection of pH *and Wavelength.*—At pH 4·3 alizarin complexone, which behaves as an acid–base indicator, just begins its transition from yellow to red; this pH was used throughout; the effect of using higher pH ranges was not studied. Determination of the optical density at varying wavelengths showed that 610 mμ was the most suitable wavelength for measurement of the fluoride complex. The calibration curve is linear over the range 8 to 35 μg. of fluoride, but its projection does not pass through the origin.

Results are included in the Table. Amounts of sample of the order of 100 μg. were used.

Compound	Fluorine (%) Calc.	Found	Error (%)	No. of detns.	Range of errors (%) Max.	Min.
Sodium fluoride	45·30	45·26	−0·04	24	−0·90	0·0
p-Fluorobenzoic acid	13·6	13·9	−0·30	9	±0·50	0·0
S-Benzylthiuronium heptafluoroadipate	22·0	21·7	−0·30	5	−0·60	−0·10
Research compound A	18·7	18·4	−0·30	7	−0·8	−0·10
Research compound B	9·49	9·36	−0·13	5	−0·24	+0·11
Research compound C	24·45	24·47	−0·03	3	−0·25	−0·05
Tetra-*p*-fluorophenylethylene	18·80	18·77	−0·03	7	−0·60	0·0
Trifluoroacetanilide	30·10	30·23	+0·13	4	+0·30	±0·20
S-Benzylthiuronium hexafluoroadipate	19·4	19·3	−0·10	5	+0·20	−0·60
$[CF_3 \cdot C_6H_4 \cdot P(C_2H_5)_2]_2CuI$	19·2	19·5	+0·30	3	−0·20	+0·60
$CF_3 \cdot C_6H_4 \cdot P(C_2H_5)_2CdI_2$	9·49	9·36	−0·13	4	−0·24	+0·11
m-Trifluoromethylbenzoic acid	30·00	29·81	−0·19	6	+0·10	−0·60

Experimental

Apparatus.—Optical density was measured on a Unicam SP.600 visual-range spectrophotometer. A 12v heavy duty battery was used to supply the current, since fluctuations of the A.C. mains were not eliminated sufficiently by the 12v transformer normally used.

Conical flasks (250 ml.) with B24 joints and stoppers were used for decomposition of the sample. The stoppers were fitted with 1 mm. diameter platinum wire for clamping the sample in position. These flasks are standard equipment and have been described in detail elsewhere.[7]

Solutions.—(1) 0·0005M-*Alizarin complexone.* 0·481 g. of pure alizarin complexone was transferred to a standard 2 l. flask, suspended in *ca.* 100 ml. of water, and dissolved by the addition of a minimum of fresh dilute sodium hydroxide solution. The solution was diluted to 1 l. and 0·5 g. of sodium acetate was added. Dilute hydrochloric acid was carefully added to bring the pH to *ca.* 5·0 (thin layer of solution pink). The solution was then diluted to the mark and transferred to a clean, dry, brown-glass vessel together with a further 500 ml. of water.

[8] Francis, personal communication; Senkowski, Wollish, and Shafer, *Analyt. Chem.*, 1959, **31**, 1574; Steyermark and Kaup, personal communication.

(2) 0·0005M-*Cerous nitrate.* 0·02M-Cerous nitrate solution was standardised by direct titration at pH *ca.* 6·0 with standard EDTA; Xylenol Orange was used as indicator. The correct volume of this solution was diluted to yield 2·5 l. of 0·0005M-Ce^{III}. The solution was transferred to a clean, dry vessel together with *ca.* 5·0 mg. of hydroxylamine hydrochloride.

(3) pH 4·3 *Acetate buffer.* 105 g. of hydrated sodium acetate and 100 ml. of glacial acetic acid were diluted to 1 l.

(4) *Fluoride solution, 100 μg. per ml.* 0·2211 g. of B.D.H. sodium fluoride (extra pure) was dissolved in water, diluted to 1 l., and stored in a Polythene bottle.

(5) *Fluoride solution, 5·0 μg. per ml.* 50 ml. of solution (4) were diluted to 1 l. and stored in a Polythene bottle.

Standard Curve.—A standard curve was constructed by weighing, on the submicro-balance, samples of pure, dry sodium fluoride whose weights lay between the limits of 20 and 90 μg. This gave a range of fluoride 10—40 μg. The samples were transferred to clean six-inch test tubes and dissolved in a little water.

Into a 100 ml. standard flask were introduced 10 ml. of 0·0005M-alizarin complexone solution, the fluoride solution, and washings from the tube; 2 ml. of pH 4·3 buffer were added and the solution diluted to *ca.* 75 ml. 10 ml. of 0·0005M-Ce^{III} were added with swirling; the solution was diluted to 100 ml., and was stored for 1 hr. in a box to protect it from light and draughts.

The optical densities of these solutions were measured in 4 cm. cells at a wavelength of 610 mμ by use of the blue-sensitive photo-cell against a blank solution containing only reagents. The standard curve was reproducible, but as a precaution against instrumental variation was checked against sodium fluoride with each series of determinations.

Procedure.—Samples of the compound previously dried over phosphoric oxide and sufficient to give 10—40 μg. of fluorine on combustion was transferred to a piece of ashless filter paper of the usual shape and size.[5] After deposition of the solid the paper was folded completely, doubled at right angles to the original folds, and rolled up into a cylinder to fit into the platinum spiral. The paper was lighted and burned off in a 250 ml. flask containing *ca.* 30 ml. of distilled water and an atmosphere of oxygen. After combustion, which should leave no carbonaceous residue, the solution was kept with occasional shaking for 10 min. The resulting solution was then treated as described in the preparation of the standard curve.

When the compound contains $-CF_3$ groups, the sample should be covered with 1 mg. of potassium chlorate before it is folded in the paper.

One of us (M. A. L.) thanks the D.S.I.R. for a research grant.

CHEMISTRY DEPT., THE UNIVERSITY, BIRMINGHAM. [*Received, May 4th,* 1959.]

---

718. *The Kinetics of Formation of Some Polyesters.*

By M. T. POPE and R. J. P. WILLIAMS.

The kinetics of the condensation polymerisation of adipic acid with diethylene glycol, catalysed by toluene-*p*-sulphonic acid, are of simple second order after an initial period in which they are more complex. The early stages in the reaction at 140° occur at a greater rate than the later steps but the situation is more confused at lower temperatures. The molecular-weight distributions in the polymers are examined and discussed.

CONDENSATION polymerisation between dibasic acids, $[CH_2]_n(CO_2H)_2$, and dihydric alcohols, $[CH_2]_n(OH)_2$, leads to linear polyesters of considerable molecular weight. The kinetics of the acid-catalysed esterifications such as those of the reaction between adipic acid and diethylene glycol have been described by Flory [1] who was able to explain the later stages of the reaction leading to a wide range of high polymers of molecular weight from a few hundred up to 10,000. On the other hand, he was unable to account for the initial stages of the reaction leading to polymers of molecular weight below about 500. The present investigation was designed to study these early stages of reaction.

[1] Flory, *J. Amer. Chem. Soc.*, 1940, **62**, 1057.

Experimental

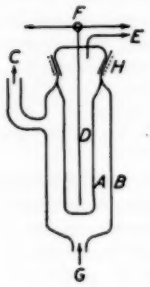
Materials.—Purified adipic acid, recrystallised from water, had m. p. 154·0—154·5°. Diethylene glycol was fractionally distilled at low pressure, b. p. 133°/14 mm. Both compounds were stored in a vacuum desiccator. The catalyst, crystalline toluene-*p*-sulphonic acid tetrahydrate, was not purified.

Apparatus and Method.—The reaction, which was studied in the melt, is

$$HO_2C\cdot[CH_2]_4\cdot CO_2H + HO\cdot[CH_2]_2\cdot O\cdot[CH_2]_2\cdot OH \longrightarrow HO_2C\cdot[CH_2]_4\cdot CO\cdot O\cdot[CH_2]_2\cdot O\cdot[CH_2]_2\cdot OH + H_2O$$

The extent of this reaction was found at different times by three techniques: (*a*) measuring the water liberated, (*b*) determining the bulk viscosity of the melt, and (*c*) titrating the residual acid end groups. The second method was calibrated by the third. The same apparatus, used in all the polymerisations (Fig. 1) and similar to that employed by Flory,[2] consisted of a reaction finger, *A*, kept at a constant temperature in the vapour jacket, *B*, which was connected to a condenser, *C*. Purified, oxygen-free nitrogen was bubbled into the finger through a capillary, *D*. The nitrogen stirred the polymer and carried water into the trap *E*. The top of the trap was heated electrically so that the water was completely removed. The water liberated was determined by weighing the trap at different times. The nitrogen supply was cut off from time to time at the two-way tap, *F*, and the capillary then connected to a suction pump so that polymer could be drawn up the capillary, *D*. After the suction had been turned off and the capillary opened to the atmosphere, the time of fall of the meniscus of the fluid polymer was measured between two marks on the capillary. The nitrogen flow was then resumed. The time of fall was related to the bulk viscosity of the polymer, η, by a previous calibration of the capillary with liquids of standard bulk viscosity. The reaction was stopped at any desired time by rapid cooling of the contents of the finger. The residual acid end groups of the final polymer were then determined by titration in acetone or acetone–ethanol with aqueous alkali and α-naphtholphthalein as indicator. This gave M_n or z_n, the number-average molecular weight and chain length respectively. For polymers of high molecular weight we have shown that the molecular-weight distribution is that of the most probable distribution.[3] Thus $M_n = M_w/2$ and $z_n = z_w/2$ where w refers to the weight average. Determination of M_n and the bulk viscosity of the final polymers therefore permitted us, following Flory,[1] to establish the relationships: (1) $\log \eta = -1{\cdot}92 + 0{\cdot}120 z_w^{\frac{1}{2}}$ at 140°; (2) $\log \eta = -1{\cdot}21 + 0{\cdot}099 z_w^{\frac{1}{2}}$ at 109°. Flory gave $\log \eta = -1{\cdot}04 + 0{\cdot}099 z_w^{\frac{1}{2}}$ at 109°. The relationships were used to find the extent ofpolymerisation at any time in a polymerisation from the bulk viscosity, η.

Fig. 1. *Apparatus.*



Kinetics.—In Fig. 2 we plot time against x_n, the degree of polymerisation given by $z_n = zx_n + 1$, where z is the number of chain atoms per polymer segment. Except at low degrees of polymerisation the observations fit Flory's equation $C_0 C_{cat} kt = x_n + 1$, where C_0 is the initial concentration of reactants, C_{cat} is the concentration of catalyst, and k is a true third-order rate constant. At 140° the value of $C_{cat}k$ was 0·95 mole^{-1} l.sec.$^{-1}$ over the linear part of the plot in Fig. 2. By following the rate of evolution of water over the earliest part of the reaction (Fig. 3) we again observed that Flory's equation was true but the constant $C_{cat}k$ was 1·50 mole^{-1} l. sec.$^{-1}$. The reaction proceeds more rapidly at low degrees of conversion. Such an observation implies that the molecular-weight distribution at low degrees of conversion should be different from the most probable distribution. Studies of the amounts of adipic acid in the polymers and of the molecular-weight distribution confirm this.

Concentration of Adipic Acid in the Polymers.—Adipic acid was determined by a modification of the method described by Kröller.[4] Two solutions were made up in ethanol; (*a*) contained 0·50 g. of polymer in 5·0 ml., and (*b*) contained 0·01 g. of adipic acid in the same volume of solvent. To each were added 5 ml. of a 5·0% ethanolic solution of mercuric acetate containing five drops of N-acetic acid. A crystalline precipitate was rapidly formed in (*b*) but (*a*) remained clear. Further experiments demonstrated that 0·0003 g. of adipic acid when added to 0·5 g. of

[2] Flory, *J. Amer. Chem. Soc.*, 1939, **61**, 3334.
[3] Pope, Weakley, and Williams, *J.*, 1959, 3442.
[4] Kröller, *Deut. Lebensm. Rundschau*, 1947, **43**, 1.

the same polymer as in solution (*a*) could be detected by the test. A simple calculation from the known molecular weight of the polymer showed that if the rate of polymerisation had remained constant throughout the whole extent of the polymerisation, *i.e.*, if the polymer had the most probable distribution, solution (*a*) should have contained 0·0985 g. of uncombined adipic acid. The above experiment demonstrated that there was less than 0·3% of this amount present, a result confirming the view that the early stages of the reaction were more rapid than the subsequent stages. The analysis was repeated on several polymers with the same result.

FIG. 2. *Change of degree of polymerisation, x_n, with time at (A) 140°, (B) 124·5°, (C) 109°.*

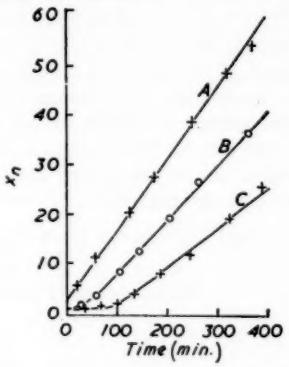


FIG. 3. *Evolution of water during polymerisation. Three separate experiments are illustrated in order to demonstrate reproducibility. The broken line is the theoretical maximum.*

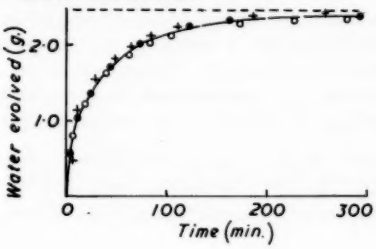


FIG. 4. *Molecular-weight distributions in polyesters of four different average molecular weights: A, 375; B, 570; C, 870; D, 1760.*

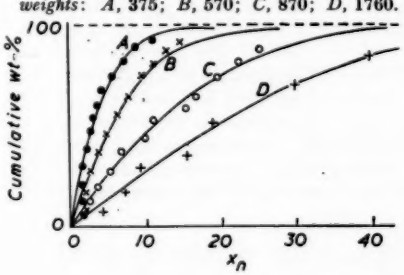
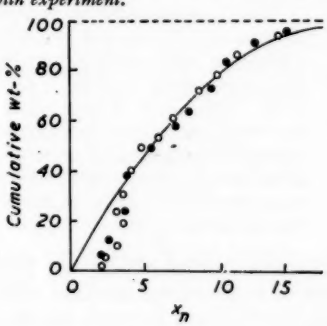


FIG. 5. *Molecular-weight distribution in two polymers of the same average molecular weight, 570, but prepared at different temperatures. The full line is a theoretical most probable distribution drawn to be a good fit with experiment.*



Distribution of Molecular Weight in the Polyesters.—Details of the method of polymer analysis are given elsewhere.[3,5] The molecular-weight distributions of the higher-molecular weight polymers agree well with theory (Fig. 4). The deviations from the most probable distribution in the lower polymers is such that low-molecular weight material has been lost at the expense of higher-molecular weight polymers. This is the distribution to be expected if the earlier stages in the reaction are faster than the later.

Because the differences in kinetics at different temperatures were so marked (Fig. 2) we analysed polymers of the same number-average molecular weight but prepared at different temperatures. Fig. 5 shows that we were unable to see any differences in the molecular-weight distributions.

[5] Baker and Williams, *J.*, 1956, 2352.

XUM

Discussion

The present work confirms Flory's,[1] in so far as the kinetics of formation of polyesters are given by his equation $C_0C_{cat}kt = x_n + 1$ over the range of polymers of molecular weight from some hundred to several thousand. The equation implies that the reactivity of the end groups is unaltered by the changes in the medium during reaction. The molecular-weight distributions of the low-molecular weight polymers are not those expected from equal reactivity of the end groups. The deviations in distribution from the most probable distribution and the kinetics at 140° both show that the low-molecular weight polymers react most rapidly. Moreover the same distribution is observed for polymers prepared at lower temperatures where the kinetics (Fig. 2) indicate a slower reaction rather than a faster one at low degrees of polymerisation. Flory [1] also observed that the initial stages of reaction were slower than the later, and he pointed out that this was common to simple esterification also. He concluded that the changes in kinetics were due to changes in the characteristics of the medium and that there were no changes in the reactivity of the functional groups. Although we cannot agree with the latter conclusion we are unable to offer any alternative explanation to an effect of the medium for the changes in kinetics of reaction with temperature and time in the early stages. If we are correct the changes in medium on increase of molecular weight serve to increase the reactivity.

One of us (M. T. P.) is indebted to Courtauld's Scientific and Educational Trust Fund for a Scholarship. We thank Mrs. Y. P. Dick for assistance.

Inorganic Chemistry Laboratory, Oxford. [*Received, January 6th*, 1959.]

---

719. *The Conductance of Solutions in which the Solvent Molecule is "Large." Part IV.*[1] *Amine Picrates in Triethyl Phosphate.*

By C. M. French, P. B. Hart, and D. F. Muggleton.

The conductances in triethyl phosphate at 40° of three quaternary ammonium picrates and two amine picrates have been measured in the concentration range $4{\cdot}59 \times 10^{-6}$ to $6{\cdot}10 \times 10^{-4}$N. One of the systems was studied also at 25° and 55°. All solutes behaved as moderately strong electrolytes. The ratios to each other of the limiting equivalent conductances of the three quaternary ammonium picrates were fairly close to the values in solvents having smaller molecules, *e.g.*, acetonitrile. Walden products were unexpectedly high, and anomalies were encountered in the ion-pair dissociation constants. Ionic rather than molecular dissociation was observed for the two amine picrates.

Tritolyl and trioctyl phosphates have already been used to study the electrical conductance of non-aqueous systems where the solvent molecules are larger than those of common solvents, and the work has now been extended to solutions in triethyl phosphate. This solvent has much smaller molecules than the phosphoric esters employed earlier [1] so that the effect of chemical nature and structure, as opposed to mere molecular size, might become dominant factors. Conductance relationships in this solvent might therefore be expected to approximate to those of solutions in solvents of conventional size.

Experimental

Solutes were purified and conductances measured as described earlier.[1]

Triethyl phosphate was dried (Na_2SO_4), and distilled under reduced pressure. The middle fraction (~80%) was stored for several weeks over anhydrous sodium sulphate, again fractionated, and repeatedly distilled under reduced pressure until the specific conductance reached a constant

[1] Part III, French and Muggleton, *J.*, 1957, 5064.

low value [b. p. 216°/760 mm. (lit.,[2] 216°/760 mm.), 70·5°/4 mm. (lit.,[3] 75·5°/5 mm.); n_D^{20} 1·40527 (lit.,[2] n_D^{20} 1·4053); d_4^{25} 1·06826 (lit.,[2] 1·0686), d_4^{40} 1·05332 (lit.,[2] 1·0532), d_4^{55} 1·03841 (lit.,[2] 1·0378); viscosity η^{25} 2·147, η^{40} 1·684, η^{55} 1·376 cP; dielectric constant ε^{15} 13·43, ε^{25} 12·94, ε^{45} 11·91, ε^{65} 10·93; specific conductance $\times 10^8$, κ^{25} 1·19, κ^{40} 1·68, κ^{55} 2·89 ohm^{-1} cm.$^{-1}$].

Difficulties were encountered in measuring the dielectric constant of triethyl phosphate because the ester appears to have a high dielectric loss. The Schering bridge previously used failed because the capacitance to be measured (C_p) will be equal to $-\Delta C_1$, the change in capacitance of the variable condenser C_1 (in parallel with the test cell) which is required to restore balance when the test cell is introduced into the circuit, only if $R_p \gg R_4$, where R_p is the resistance of the test cell, and R_4 the resistance in parallel with a small variable capacitance C_4, itself in series with C_1. When the conductance of the liquid in the test cell is high, $-\Delta C_1 < C_p$, and the measured dielectric constant will be too small. A precise estimate cannot be given of the conductance of the liquid above which the method fails, but experience suggests that a specific conductance of 5×10^{-10} ohm^{-1} cm.$^{-1}$ is probably near the limit. Extrapolation of measurements made by a high-frequency technique also gave unacceptable results.

The dielectric constant of triethyl phosphate was finally measured by a resonance method, in an apparatus built by Mr. Fairbourne of this Department according to his modification of

TABLE 1. *Equivalent conductance in triethyl phosphate.*

10^4c	Λ	10^4c	Λ	10^4c	Λ	10^4c	Λ	10^4c	Λ
Et_4NPic at 25°									
61·032	20·591	17·132	25·361	6·3999	28·672	1·7836	33·732	0·27158	36·071
36·696	22·426	12·216	26·565	3·8992	30·488	1·5161	33·187	0·050588	37·549
22·451	24·323	7·8264	28·063	2·9085	31·390	0·81695	34·448		
Et_4NPic at 40°									
46·423	27·010	18·197	31·146	6·0198	36·551	1·7897	40·823	0·82821	43·162
40·939	27·426	12·372	33·193	5·2246	37·004	1·4314	41·504	0·33193	45·333
27·650	29·471	8·8596	34·750	3·5424	38·711	0·96780	42·927	0·17942	46·861
								0·11885	47·394
Et_4NPic at 55°									
39·531	32·947	9·4458	41·503	2·4734	48·800	0·81734	53·052	0·15565	56·112
21·525	36·239	5·7580	44·427	1·5478	50·648	0·64240	53·468	0·045871	57·668
17·798	37·554	4·5970	45·876						
Bu_4NPic at 40°									
34·448	24·657	18·219	27·704	7·1039	31·618	2·6077	35·526	0·55098	39·569
31·359	25·163	11·467	29·643	3·7666	34·385	2·0081	36·540	0·51470	39·446
28·147	25·535	7·1945	31·837	2·6515	35·635	1·0270	38·173	0·31270	40·121
$(C_5H_{11})_4NPic$ at 40°									
34·620	23·667	15·173	27·384	7·5455	30·361	2·5062	34·506	0·35425	38·825
26·041	24·813	11·336	28·512	5·2900	31·822	1·8893	35·261	0·27157	39·250
22·779	25·598	9·8013	29·285	4·9109	32·278	0·92391	37·352		
$(Ph{\cdot}CH_2)_3NHPic$ at 40°									
31·038	22·074	7·2938	27·193	1·1827	36·465	0·78434	39·180	0·19501	42·425
16·763	23·701	5·0410	28·579	0·80032	39·154	0·44933	40·591	0·12341	42·644
11·425	25·376	2·9751	31·092						
$Ph{\cdot}NH_2Pi$ at 40°									
56·928	17·974	15·116	22·804	7·0898	27·061	1·9315	34·306	0·66991	38·352
34·807	19·163	12·172	23·870	4·4991	29·790	1·2969	36·114	0·31233	40·358
25·932	20·340	8·9941	25·508	3·1022	31·897	0·98275	37·209	0·06540	42·723
19·195	21·747								

Le Fèvre and Calderbank's circuit.[4] A test cell as described by Smith [5] was used, the leads to it being unscreened and kept as short as possible. Ethylene dichloride, purified by refluxing over activated alumina and fractionation, was used for calibration, its dielectric constant at 25° being taken as 10·25.[6] It was not practicable to measure the dielectric constant at the three

[2] Sugden, Read, and Wilkins, *J.*, 1925, **127**, 1525.
[3] Vogel and Cowan, *J.*, 1943, 16.
[4] Le Fèvre and Calderbank, *J.*, 1948, 1951.
[5] Smith, "Dipole Moments," Butterworths, London, 1956.
[6] Fuoss and Kraus, *J. Amer. Chem. Soc.*, 1933, **55**, 3614.

temperatures used in the conductance experiments, but a plot of dielectric constant against temperature was linear, so that values at 40° and 55° were interpolated (ε^{40} 12·18, ε^{55} 11·43).

Results.—The equivalent conductance in triethyl phosphate of the five picrates at various concentrations is shown in Table 1.

Discussion

The specific conductance of solutions in triethyl phosphate varied almost linearly with concentration. This resembled the behaviour of solutions of the same salts in acetonitrile [7] but was unlike that of solutions in the phosphoric esters with larger molecules.[1] As in the case of solutions in tritolyl phosphate, however, the variation in equivalent conductance with concentration was small for all electrolytes. The Λ–$c^{\frac{1}{2}}$ plots were again shallow curves typical of moderately strong electrolytes, and could be extrapolated to give approximate values of Λ_0 from which the final values of Λ_0 shown in Table 2 were obtained by Shedlovsky's extrapolation method.[8] Consideration was also given to the modified derivation of constants from conductance data suggested recently by Fuoss,[9] but in view of the low ion-pair dissociation constants ($\leqslant 10^{-3}$) of all solutes in triethyl phosphate, and the fact that the size of the ionic species was comparable with that of the solvent, his treatment was not employed. As expected, no minima were observed in the Λ–$c^{\frac{1}{2}}$ plots since Walden's empirical rule $\varepsilon^3/c_{\text{min.}} = 3 \times 10^4$, indicated that these should occur at concentrations in excess of 10^{-2}N, and hence outside the present range.

The ratios of Λ_0 for the three tetra-alkylammonium picrates resemble those in acetonitrile [7] and other solvents with small molecules [$Et_4NPic : Bu^n{}_4NPic : (n\text{-}C_5H_{11})_4NPic$ 1 : 0·878 : 0·860], but differ markedly from the corresponding values in the other phosphoric esters. For the tetra-alkylammonium picrates in triethyl phosphate Λ_0 values differ considerably from those in tritolyl and trioctyl phosphates, and are of the order of 100 times larger, approximating more closely to values in conventional solvents. The Walden products (Table 2) are very high compared with the average values in a large number of other common solvents of conventional size, where $\Lambda_0\eta$ at 25° is 0·560 for Et_4NPic and is somewhat lower for the larger solutes. However, as with solutions in dialkyl phthalates [10] where the solvent molecules are comparatively large, the Walden product decreases with increasing size of quaternary ammonium ions, whilst $\Lambda_0\eta$ for a given salt appears to decrease with increasing solvent size. It has been suggested [10] that a "normal" Walden product may be due to uniform solvation, so that the high Walden products found in the triethyl phosphate systems indicate very limited solvation. This suggests that, as with dimethyl phthalate, the solvent molecules may be oriented with their dipoles close together and shielded from interaction with the solute ions. The large hydrocarbon residues in trioctyl and tritolyl phosphates might, however, diminish loose dipolar association of solvent molecules and hence favour increased ion solvation, thus producing the observed lowering of the Walden product. Limited solvation of the tetra-alkylammonium ions in triethyl phosphate is consistent with the fact that temperature has little effect on the Walden product, which suggests that increased ion mobility is associated simply with decreased viscosity of the solvent.

Ion-pair radii, the Bjerrum "*a*" parameter, calculated from the equation where K is the ion-pair dissociation constant (see Table 2):

$$\frac{1}{K} = \frac{4\pi N}{1000}\left[\frac{e^2|z_1z_2|}{\varepsilon kT}\right]^3 \cdot Q(b)$$

are given in Table 3 together with the corresponding values in the other phosphoric esters [1] and in acetonitrile.[7] The magnitude of "*a*" for tetraethylammonium picrate in triethyl phosphate, the smallest of the phosphoric esters, approximates closely to that in the small

[7] French and Muggleton, *J.*, 1957, 2131.
[8] Shedlovsky, *J. Franklin Inst.*, 1938, **225**, 739.
[9] Fuoss, *J. Amer. Chem. Soc.*, 1957, **79**, 3301.
[10] French and Singer, *J.*, 1956, 1424, 2428.

solvent acetonitrile at the only temperature available for comparison, but differs markedly from that in the other two phosphates. Thus, if this parameter is taken as indicating the size of an ion, the variation in value seems to indicate that the tetraethylammonium ion is solvated in each of the solvents, and perhaps also that there are differences in degree of solvation, and/or to reflect the size of the solvating molecules. Nevertheless, the change

TABLE 2.

	Et_4NPic			Bu_4NPic	$(C_5H_{11})_4NPic$	$(Ph{\cdot}CH_2)_3NHPic$	$Ph{\cdot}NH_3Pic$
	25°	40°	55°	40°	40°	40°	40°
Λ_0	37·3	47·45	57·6	41·7	40·8	44·25	43·5
$\Lambda_0\gamma$	0·801	0·799	0·793	0·702	0·687	0·745	0·732
10^4K ...	11·55	10·97	10·16	12·59	10·81	5·30	4·19

TABLE 3. *Ion-pair size* (Å).

	Solute				
		Et_4NPic		Bu_4NPic	$(C_5H_{11})_4NPic$
Solvent	25°	40°	55°	40°	40°
Triethyl phosphate	6·15	7·00	7·92	7·90	6·78
Trioctyl phosphate	9·10	8·41	7·86	10·60	10·64
Tritolyl phosphate	9·59	11·50	16·00	36·04	38·09
Acetonitrile	6·00				

in "*a*" with temperature indicates that other factors must also be involved. The interaction energy between a large ion and the solvent will be small so that a slight increase in temperature should produce a significant decrease in solvation. However, "*a*" increases with temperature in both triethyl and tritolyl phosphate although the expected decrease is observed in trioctyl phosphate. Finally the ion-pair radius in triethyl phosphate increases slightly on passing from tetraethyl- to tetrabutyl-ammonium picrate and then decreases although this does not occur in the other two solvents. This again suggests a very small degree of solvation of quaternary ammonium ions in triethyl phosphate, the observed difference of 0·92 Å in "*a*" between the tetraethyl- and tetrabutyl-ammonium picrates possibly representing the difference in sizes of the actual quaternary ammonium ions (the difference calculated by Robinson and Stokes [11] from models is 0·94 Å), the smaller value of the third salt corresponding to a decrease in solvation. These arguments do not exclude the possibility that the picrate ion also is solvated in these solvents, and some of the phenomena just discussed may be due in part, at least, to this cause. Nevertheless, since the picrate ion is common to all solutes here used, solvation of this ion cannot account for all the variations in "*a*" noted.

These data may also be considered in terms of the ion-pair dissociation constants, and these, for all three quaternary ammonium salts in triethyl phosphate, are similar to those in tritolyl phosphate, but differ considerably from those in trioctyl phosphate. The low dissociation constant of tetrapentylammonium picrate compared with that of the preceding homologue may clearly be associated with the decreased solvation of the cation discussed above, and the consequent possibility of closer approach of the two ions of the ion pair. The increase in K between tetraethyl- and tetrabutyl-ammonium picrate parallels qualitatively the effects in the other two phosphoric esters,[1] although the ratio of K for the two salts in triethyl phosphate approaches much more nearly the value in conventional solvents. Finally, contrary to Kraus's suggestion,[12] K and ε decrease with increasing temperature for solutions in both triethyl and trioctyl phosphates.

It is noteworthy that, in triethyl phosphate, Λ_0 for both tribenzylammonium and anilinium picrates is similar to the values for the quaternary ammonium picrates. It seems therefore, that the acid–base (*i.e.*, molecular) dissociation which has been postulated to account for the conductimetric behaviour of these two amine picrates in most other solvents

[11] Robinson and Stokes, "Electrolyte Solutions," Butterworths, London, 1955.
[12] Kraus, *J. Phys. Chem.*, 1956, **60**, 129.

is negligible in triethyl phosphate. Tribenzylammonium picrate in acetonitrile [7] is also an exception, and Marryott,[13] by dielectric measurements, failed to find evidence of acid–base dissociation of this electrolyte in benzene. It appears also that the mobility of the tribenzylammonium ion, with 24 carbon atoms, is greater than that of the tetrapentylammonium ion with only 22 carbon atoms, Λ_0 for the two picrates being 44·2 and 40·8 respectively. However, the Shedlovsky plots for tribenzylammonium picrate were somewhat less reliable than in the other cases, deviations from linearity occurring at a considerably lower concentration.

The authors thank the University of London Central Research Fund Committee, the Royal Society, and the Chemical Society for grants, and Dr. R. F. Hudson for the loan of dielectric constant apparatus. One of us (D. F. M.) thanks the Department of Scientific and Industrial Research for a maintenance grant, and one (P. B. H.) the Governors of this College and the Ministry of Education for a supplemented Research Studentship.

QUEEN MARY COLLEGE, MILE END ROAD,
LONDON, E.1.

[*Received, April 10th,* 1959.]

[13] Marryott, *J. Res. Nat. Bur. Stand.*, 1948, **41**, No. 1, 7.

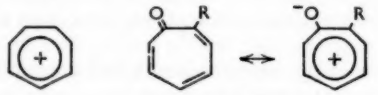
---

720. *Tropolones. Part X.* Synthesis and Properties of 2,3-Benzotropone.*

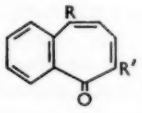
By G. L. BUCHANAN and D. R. LOCKHART.

A practicable route to 2,3-benzotropone is described; the properties and reactions of this substance indicate that it behaves rather as a conjugated dienone than as an aromatic compound.

THE widely accepted view [1] that tropolone, as a derivative of the tropylium ion (I), owes its aromatic character largely to the participation of tropylium structures in the resonance picture (II), is supported by *X*-ray,[2] electron-diffraction,[3] and dipole moment [4] measurements. Although it has been stated [5] that tropone (III) is also aromatic, we know of no compelling chemical evidence which supports this opinion and the work which we now describe contradicts it.



(I) (II) R = OH (III) R = H



	R	R′
(IV)	OH	H
(V)	H	H
(VI)	H	OH

Our object was, first, to find a practicable synthesis of a tropone, and then to examine its properties for evidence of aromaticity. For this, we selected the known [6] 2,3-benzotropone (V). Although the benzene nucleus will modify the properties of the tropone ring,

* Part IX, *J.*, 1956, 2620.

[1] Schaeppi, Schmid, Heilbronner, and Eschenmoser, *Helv. Chim. Acta*, 1955, **38**, 1874; Doering and Knox, *J. Amer. Chem. Soc.*, 1952, **74**, 5683; Baker and McOmie, "Progress in Organic Chemistry," ed. J. W. Cook, Butterworths, London, 1955, Vol. III, p. 44; Nozoe, "Progress in the Chemistry of Organic Natural Products," Springer, Vienna, 1956, Vol. XIII, p. 235.

[2] Robertson, *J.*, 1951, 1222.

[3] Kimura and Kubo, *Bull. Chem. Soc. Japan*, 1953, **26**, 250.

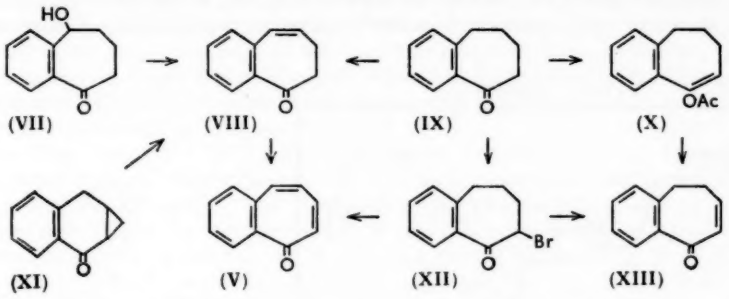
[4] Kurita, Nozoe, and Kubo, *ibid.*, 1951, **24**, 10; Di Giacomo and Smyth, *J. Amer. Chem. Soc.*, 1952, **74**, 4411.

[5] *Ann. Reports*, 1956, **53**, 149; Baker and Ollis, *Quart. Rev.*, 1957, **11**, 15; Heusner, *Angew. Chem.*, 1958, **70**, 643; Nozoe, *Experientia*, Suppl. 7, 1957, 313.

[6] Rennhard, Di Modica, Simon, Heilbronner, and Eschenmoser, *Helv. Chim. Acta*, 1957, **40**, 257.

we shall compare this ketone with its hydroxy-derivatives [7,8] (IV) and (VI), in both of which the aromatic character is similarly diminished but certainly not extinguished.

The original synthesis [6] of 2,3-benzotropone is tedious, and we have developed a superior route from the ketone (IX). First we prepared 2,3-benzocyclohepta-2,6-dienone (XIII) [ν(C=O) 1660 cm.$^{-1}$] by dehydrobromination of the α-bromo-ketone (XII) and by the action of *N*-bromosuccinimide on the enol acetate (X). However, it rapidly resinified,



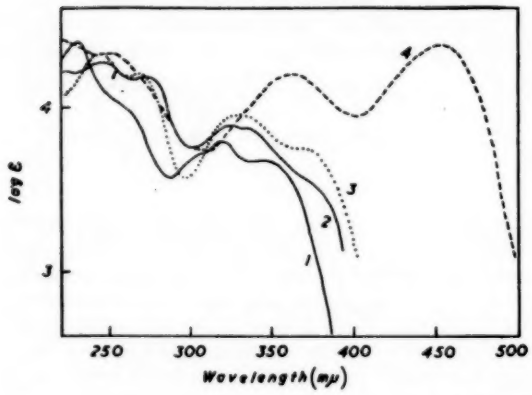
and was therefore unsuitable for further work. In contrast, the isomeric ketone (VIII) is stable. Julia [9] obtained this by base-catalysed rearrangement of the cyclopropyl ketone (XI) and established the presence, but not the position, of an ethylenic group by reduction to 2,3-benzocyclohept-2-enone. We obtained the same unsaturated ketone by dehydration of the known keto-alcohol [10] (VII) by boric acid or, more conveniently, by bromination of 2,3-benzocyclohept-2-enone followed by dehydrobromination: these transformations establish the position of the double bond. We are grateful to Dr. Julia for supplying details of his work in advance of publication. The unsaturated ketone (VIII) is readily oxidised to 2,3-benzotropone by selenium dioxide, and was identified by comparison of its 2,4-dinitrophenylhydrazone and picrate with authentic samples kindly supplied by Dr. Eschenmoser.[6] Alternatively, when Julia's ketone (VIII) is brominated, the product spontaneously eliminates hydrogen bromide, at the temperature of the reaction, affording 2,3-benzotropone. This avoids the disadvantages of the selenium dioxide reaction, and represents a feasible route to the tropone. We have found it more convenient, however, to brominate the α-bromo-ketone (XII) in the benzyl position by *N*-bromosuccinimide and to dehydrobrominate the product by means of base. This procedure, which was independently employed by Elad and Ginsburg [11] on a related ketone, afforded 2,3-benzotropone from 2,3-benzocyclohept-2-enone in 65% (overall) yield, as a pale yellow oil which could be stored unchanged at 0°.

In common with other tropones, 2,3-benzotropone forms a 2,4-dinitrophenylhydrazone under normal conditions. Nevertheless, the carbonyl group is not completely normal. There are only three infrared carbonyl bands, at 1642, 1612, and 1590 cm.$^{-1}$; and although it is not possible to allocate the carbonyl stretching frequency with certainty,[6] even the highest figure is abnormally low. 2,3-Benzotropone also behaves as a base, forming a crystalline picrate and hydrobromide, and dissolves in concentrated sulphuric acid, producing the yellow tropylium cation (XIV), and it can be regenerated by diluting the acid solution with water; even after 10 minutes' boiling in concentrated sulphuric acid, 2,3-benzotropone is recovered on addition of water. Its ultraviolet absorption spectrum, and that of the tropylium ion (XIV), are shown in Figs. 1 and 2. 2,3-Benzotropone consumes exactly 2 mols. of bromine without evolution of hydrogen bromide; during the addition

[7] Buchanan, *J.*, 1954, 1060.
[8] Cook, Gibb, Raphael, and Somerville, *J.*, 1952, 603.
[9] Julia, *Compt. rend.*, 1955, **241**, 882.
[10] Buchanan and Sutherland, *J.*, 1956, 2620.
[11] Elad and Ginsburg, *J.*, 1957, 1286.

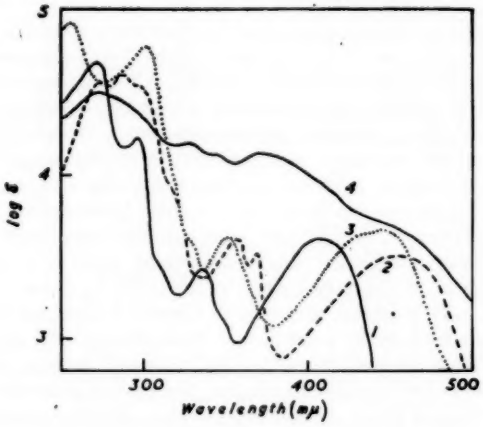
of the first mol., an orange complex is precipitated; from this, benzotropone is regenerated by water or methanol. On addition of the second mol. of bromine, the complex redissolves and removing the solvent then affords the tetrabromide (XV) [ν(C=O) 1700 cm.$^{-1}$: no C=C band above 1590 cm.$^{-1}$] which is stable at room temperature but loses hydrogen bromide at *ca.* 100° or on treatment with a base, affording a dibromotropone A, whose structure is largely revealed by the following facts. On oxidation it affords phthalic acid, showing that the bromine atoms are outside the benzene ring and excluding a (tricyclic) cyclopropane structure (such compounds resist [10] oxidative degradation). Compound A is

FIG. 1. *In ethanol.*



Absorption spectra of (1) 2,3-*benzotropone* (V), (2) 5,7-*dibromo-* (XVI), (3) 4,7-*dibromo-* (XIX), *and* (4) 5,7-*dinitro*-2,3-*benzotropone* (XX).

FIG. 2. *In* 15M-*sulphuric acid.*



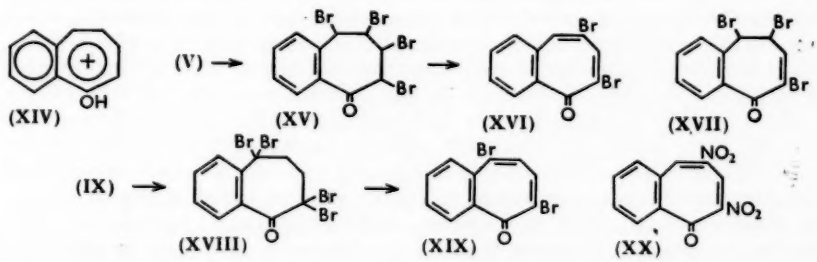
therefore most plausibly formulated as a benzotropone bearing two bromine substituents in the seven-membered ring. Like 2,3-benzotropone, it dissolves in concentrated sulphuric acid, and is reprecipitated on the addition of water, and survives treatment with *boiling* concentrated sulphuric acid, properties which are well-nigh diagnostic of the tropone ring system. Its ultraviolet spectrum (Fig. 1) is closely similar to that of 2,3-benzotropone, and in sulphuric acid the spectrum (Fig. 2) shows the same displacements and intensifications of bands as does that of 2,3-benzotropone.

If the tetrabromide is treated with one mol. of sodium hydroxide in ethanol, the comparatively stable tribromo-compound (XVII) [ν(C=O) 1665 cm.$^{-1}$] is produced, and this

must be heated to 100—120°, or treated with excess of base, before it is converted into the (same) dibromotropone. This defines the position of the ethylenic bond in compound (XVII) and excludes alternative cyclopropane structures; a structure in which the halogen atoms are vicinal may be dismissed as mechanistically improbable. When 2,3-benzotropone is treated with liquid bromine without temperature control, the product is a mixture of the tribromide (XVII) and the dibromotropone A, and the latter is the sole product of reaction between Julia's ketone (VIII) and excess of liquid bromine at 100°. It is thus clear that the ostensibly aromatic seven-membered ring in 2,3-benzotropone is sufficiently unsaturated to add two mols. of bromine, and it is noteworthy that the conjugation may be restored step-wise. It is particularly remarkable that the tribromo-intermediate (XVII) is stable, when the elimination of only a molecule of hydrogen bromide would render the molecule " aromatic."

It has been reported [12] that 2,3-benzocyclohept-2-enone (IX) with liquid bromine gives a solid product. The product, we find, is a dibromotropone B, isomeric with substance A described above. The compound B also yields phthalic acid on oxidation, and is stable in boiling concentrated sulphuric acid whence it is reprecipitated by water. Its ultraviolet spectra in ethanol and in sulphuric acid (Figs. 1 and 2) point to a close relation with isomer A and with 2,3-benzotropone; we therefore regard them both as dibromobenzotropones. It is significant that both A and B show carbonyl absorption in the infrared at $\nmid$1634 cm.$^{-1}$, although neither reacts with 2,4-dinitrophenylhydrazine under the standard conditions. Inertness of the carbonyl is characteristic of the α-substituted tropones (*e.g.*, α-bromotropones), and is some indication that one of the bromine atoms is adjacent to the carbonyl group. In the case of the dibromotropone A at least, this is consistent with its derivation from Julia's ketone (VIII), and from the tribromo-compound (XVII) whose structure has been independently argued. The position of the second bromine atom is less certain, but we visualise the formation of the two dibromotropones by the schemes, (V) ⟶ (XV) ⟶ (XVI), and (IX) ⟶ (XVIII) ⟶ (XIX), and suggest the tentative structures (XVI) and (XIX) for compounds A and B respectively. Several unsuccessful attempts were made to bring about base-catalysed ring contractions of the dibromotropones to substituted naphthoic acids: in mild conditions, starting material was recovered; more forcing conditions led to considerable decomposition.

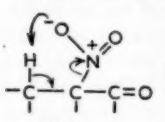
Although 2,3-benzotropone can be recovered in high yield from solution in concentrated hydrochloric or sulphuric acid, it reacts at room temperature with concentrated nitric



acid, or even with 50% aqueous nitric acid, affording a dinitro-derivative in good yield. This product does not react with 2,4-dinitrophenylhydrazine under standard conditions. Oxidation degrades it to phthalic acid, and the nitro-groups are therefore in the seven-membered ring. That the nitration product is a nitro-compound rather than a nitrite is indicated by the very intense bands at 1525 and 1332 cm.$^{-1}$ in the infrared spectrum [13]

[12] Kipping and Junter, *J.*, 1901, **79**, 602.
[13] Bellamy, " Infrared Spectra of Complex Molecules," Methuen, London, 1958, p. 227 *et seq.*

and by the failure of the diphenylamine–sulphuric acid colour reaction.[14] The oxidation evidence, the low $\nu(NO_2)$, and the absence of saturated C–H absorption in the infrared spectrum (potassium chloride disc) point to a tropone structure. Like the other tropones described above, the dinitro-compound dissolves in concentrated sulphuric acid, and is reprecipitated on dilution with water. The ultraviolet spectrum of its ethanol solution (Fig. 1) is related only in general shape to that of 2,3-benzotropone, but in that of its sulphuric acid solution (Fig. 2) no relation can be seen. Catalytic reduction of the dinitrotropone in neutral solution stopped after the uptake of only 3—4 mols. of hydrogen, but in acid solution the theoretical amount (9 mols.) was smoothly and rapidly absorbed; this behaviour is typical of nitro-olefins.[15] The product of the neutral reduction was 2,3-benzocyclohept-2-enone (IX), showing that the ring system remained intact during nitration. The benzocycloheptenone presumably arises by reduction of the diene system, elimination of nitrous acid or its equivalent, and reduction of the resulting tropone. In this case, as in the spontaneous decomposition of 1,2-dinitroalkanes,[16] the driving force is probably the achievement of conjugation (XXI). The product of the acid reduction was a water-soluble syrup, which consumed periodate but could not be further characterised. It seems unlikely that the dinitro-compound is formed by an electrophilic substitution and we regard it as an addition–elimination reaction of N_2O_4, this being produced by mutual oxidation–reduction of tropone and nitric acid. When 2,3-benzotropone is treated at 0° with a solution of dinitrogen tetroxide in carbon disulphide, an unstable intermediate can be isolated. This product spontaneously evolves dinitrogen tetroxide at room temperature, affording the same dinitro-compound in quantitative yield. By analogy with the bromine addition–elimination reaction of benzotropone, we suggest structure (XX) for the product. The dinitrotropone dissolves in aqueous alkali or sodium carbonate solution, and its ultraviolet absorption is thereby radically changed. The solubility in alkali must be ascribed to hydration of the conjugated C=C group, and consequent formation of a substituted nitrocycloalkane. Acidification of the alkaline solution afforded no identifiable product.



(XXI)

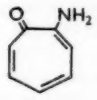
If tropones, as aromatic compounds, undergo nuclear substitutions these ought to be of a nucleophilic character; accordingly, some attempts were made to bring about amination by sodamide or hydrazine, and hydroxylation by alkali. In each instance, the tropone was either recovered or destroyed, according to the severity of the reaction conditions.

The chemistry of 2,3-benzotropone, as explored by Eschenmoser and by ourselves, provides little evidence of aromaticity in the seven-membered ring. Indeed, if we except its remarkable stability to boiling concentrated sulphuric acid—and this is in fact a property of a tropylium ion *per se*, the neutral molecule may be fairly accurately described as a conjugated dienone. In contrast to this, αβ-benzotropolone (VI) shows distinctly aromatic qualities,[8,17] and the isomeric hydroxytropone (IV) is likewise aromatic rather than olefinic.[7,10] Indeed, the remarkable influence exerted by a nuclear hydroxyl group on the character of the seven-membered ring has yet to receive a satisfactory explanation.

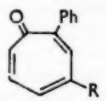
Substantially the same conclusions can be drawn from the chemistry of tropone [5,18] (III), tropolone [19] (II), and the isomeric hydroxytropones.[20] Indeed, the case for aromaticity in tropones, in terms of chemical evidence, rests entirely on amination by hydrazine or hydroxylamine. Thus tropone (III) gives the amino-derivative (XXII), and

[14] Feigl, " Spot Tests," Elsevier, Amsterdam, 1956, p. 168.
[15] Levy and Rose, *Quart. Rev.*, 1948, **1**, 385.
[16] *Idem, ibid.*, p. 382.
[17] Nozoe, Kitahara, and Ando, *Proc. Japan Acad.*, 1951, **27**, 107.
[18] Nozoe, Mukai, and Takase, *Sci. Reports Tôhoku Univ.*, 1956, **39**, 164.
[19] Pauson, *Chem. Rev.*, 1955, **55**, 9.
[20] Nozoe, Mukai, Ikegami, and Toda, *Chem. and Ind.*, 1955, 66; Coffey and Johnson, *J.*, 1958, 1741; Johns, Johnson, and Tisler, *J.*, 1954, 4605.

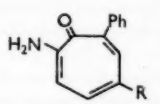
the phenyltropone (XXIII) yields [21] the amino-derivative (XXIV); in the latter case at least, cold liquid ammonia suffices to bring about the same transformation.[21] These reactions have been interpreted [21] as nucleophilic substitutions, involving a hydride-transfer step (XXVII), and the amination by ammonia presumably requires hydride-extrusion. In view of the demonstrated dienone character of tropones, it is reasonable to



(XXII)

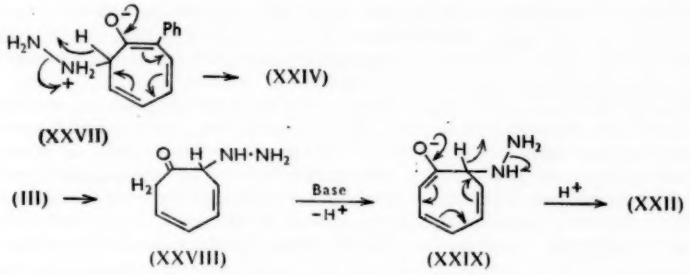


(XXIII) R = H
(XXV) R = Br



(XXIV) R = H
(XXVI) R = Br

consider an addition mechanism, *e.g.*, (III) ⟶ (XXVIII) ⟶ (XXIX) ⟶ (XXII), which utilises an essentially identical intermediate (XXIX). Such a mechanism explains adequately the reactions cited above, and explains *more* satisfactorily the remarkable



amination of the bromotropone (XXV) to (XXVI), in which the bromine atom resists nucleophilic displacement.[22] Its validity is open to dispute, but so also, we believe, is the aromatic character of tropones.

Experimental

Ultraviolet absorption spectra were measured on a Unicam S.P. 500 spectrophotometer and infrared spectra on a model 13 Perkin–Elmer double-beam instrument.

2,3-Benzocyclohepta-2,6-dienone (XIII).—(*a*) 7-Bromo-2,3-benzocyclohept-2-enone [23] (XII), b. p. 106—108°/0·05 mm. (Found: Br, 33·5. Calc. for $C_{11}H_{11}OBr$: Br, 33·65%) (2·4 g.), was heated at 170° for 1 hr. with collidine (15 ml.), cooled, treated with 6N-hydrochloric acid (50 ml.), and extracted with ether. The ethereal solution was washed with water, dried, and concentrated. The resulting pale yellow oil [ν(C=O) 1660 cm.$^{-1}$: liquid film] polymerised on storage or attempted distillation, but yielded a crimson 2,4-dinitrophenylhydrazone, which was chromatographed in benzene on alumina and, crystallised from acetic acid, had m. p. 218° (lit.,[9,23] 219°).

The bromo-ketone (XII) (2·4 g.) and 2,4-dinitrophenylhydrazine (2 g.) in acetic acid (20 ml.) containing a trace of hydrochloric acid were heated under reflux for 5 min. All solvent was then removed *in vacuo*, and the residue was chromatographed as described above, yielding the same 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 218°.

(*b*) 2,3-Benzocyclohept-2-enone (10 g.), isopropenyl acetate (50 ml.), and a few crystals of toluene-*p*-sulphonic acid were heated so that acetone slowly distilled off through a 6 inch vacuum-jacketed fractionating column. After 2 hr., no more acetone came over, and the solution was cooled, benzene (50 ml.) and 2N-sodium carbonate solution (30 ml.) were added, and the organic

[21] Nozoe, Mukai, Minigishi, and Fujisawa, *Sci. Reports Tôhoku Univ.*, 1953, **37**, 388.
[22] *Idem, ibid.*, 1954, **38**, 141.
[23] Ramirez and Kirby, *J. Amer. Chem. Soc.*, 1953, **75**, 6026.

XUM

layer was washed with water, dried, and concentrated in a vacuum. *3-Acetoxy-1,2-benzocyclohepta-1,3-diene* (X) distilled at 90—92°/0·1 mm. and had m. p. 54° (from low-boiling light petroleum) (Found: C, 77·1; H, 6·8. $C_{13}H_{14}O_2$ requires C, 77·2; H, 6·9%), ν(C=O) 1765 cm.$^{-1}$ (in CCl_4). The enol-acetate (1·5 g.) in dry chloroform (10 ml.) and carbon tetrachloride (10 ml.) was refluxed for 1 hr. with *N*-bromosuccinimide (1·37 g.) and a trace of dibenzoyl peroxide. The solution was then cooled, washed thrice with water (20 ml.), dried, and concentrated. The oily product [ν(C=O) 1660 cm.$^{-1}$] which resinified on storage or attempted distillation, afforded a crimson 2,4-dinitrophenylhydrazone identical (m. p. and mixed m. p.) with that described above.

2,3-Benzocyclohepta-2,4-dienone (VIII).—(*a*) Anhydrous t-pentyl alcohol (2 ml.) and dry benzene (18 ml.) were boiled with sodium wire (0·8 g.) for 16 hr. To the resulting solution was added 1,2,3,4-tetrahydro-1-oxo-2,3-cyclopropanonaphthalene [10] (XI) (2 g.), and heating was continued for a further 6 hr. After cooling of the solution, excess of 6N-hydrochloric acid was added, and the organic layer was separated, washed with water, dried, and distilled, affording the dienone (VIII) (60%), b. p. 146—150°/15 mm. (lit.,[9] 145°/13 mm.), $\lambda_{max.}$ (log ε) 235 (4·74), 259 (3·81), 318 (3·29), ν(C=O) 1680 cm.$^{-1}$ (film). It gave a 2,4-dinitrophenylhydazone, m. p. 217° (from acetic acid) (lit.,[9] 224°) (Found: C, 60·6; H, 4·4; N, 16·4. Calc. for $C_{17}H_{14}O_4N_4$: C, 60·5; H, 4·2; N, 16·6%).

(*b*) 4-Hydroxy-2,3-benzocyclohept-2-enone (VII) (0·75 g.) was heated for 30 min. at 160° with boric acid (1 g.) and finally distilled from the melt at 200° (bath)/15 mm. The product was identified as the enone (VIII) by comparison of infrared spectra, and afforded the 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 217°.

(*c*) 2,3-Benzosuberenone (IX) (20 g.) in dry carbon tetrachloride (100 ml.) was heated under reflux for 1 hr. with *N*-bromosuccinimide (25 g.) and a trace of dibenzoyl peroxide. The resulting solution was washed with water (3 × 100 ml.) and concentrated *in vacuo*. The oily product was then heated at 100° for 2 hr. with collidine (50 ml.). Solid material was removed, chloroform (50 ml.) was added, and the solution repeatedly extracted with 6N-hydrochloric acid, washed with water until the washings were neutral, dried, and concentrated. The product (30%), b. p. 146°/15 mm., was identified as the unsaturated ketone (VIII) from its infrared spectrum.

2,3-Benzotropone (V).—(*a*) Julia's ketone (VIII) (1 g.) in t-butyl alcohol (20 ml.) and acetic acid (3 ml.) was heated under reflux for 3 hr. with selenium dioxide (0·8 g.), cooled, and filtered. The filtrate was dissolved in ether (50 ml.) and extracted with concentrated hydrochloric acid (2 × 5 ml.). The deep yellow solution of the tropylium salt was diluted with water (10 ml.), and the resulting emulsion was extracted with chloroform (3 × 10 ml.). This extract yielded 2,3-benzotropone (300 mg.), b. p. 140°/0·1 mm., $\nu_{max.}$ (liquid film) 3510 w, 3030 m, 16040 s, 1610 s, 1588 s, 1550 s, a number of sharp bands in the finger-print region, and 3 broad, strong C–H deformation bands at 800, 770, and 710 cm.$^{-1}$. The 3510 cm.$^{-1}$ band can only be due to water, but could not be removed by distillation. The benzotropone afforded a picrate, m. p. 115—117° (from chloroform), and a magenta-coloured 2,4-dinitrophenylhydrazone, m. p. 226—228° (from acetic acid), both identical with authentic samples (m. p. and mixed m. p.), and a hydrobromide, m. p. 89° (from ethyl acetate) (Found: C, 51·4; H, 4·3; Br, 31·5. $C_{11}H_9OBr$ requires C, 51·8; H, 4·3; Br, 31·2%). A few mg. of the tropone were added to concentrated sulphuric acid and boiled for 10 min. The solution darkened, but cooling and addition of water precipitated an oil which gave a 2,4-dinitrophenylhydrazone identical (m. p. and mixed m. p.) with that derived from 2,3-benzotropone.

(*b*) *N*-Bromosuccinimide (1·7 g.) and a trace of dibenzoyl peroxide were added to 2,3-benzocyclohepta-2,4-dienone (VIII) (1·56 g.) in dry " AnalaR " carbon tetrachloride (15 ml.), and the mixture was boiled under reflux. Hydrogen bromide was evolved copiously. After 2 hr., the mixture was washed with water, dried, and concentrated under a vacuum to an oil. The infrared spectrum of this product indicated that it was incompletely dehydrobrominated. It was heated at 100° for 1 hr. with collidine (5 g.), then diluted with chloroform, and the collidine was removed by washing with 6N-hydrochloric acid. Finally, the tropone was extracted by means of concentrated hydrochloric acid, and isolated in the manner described above (yield 1·02 g.).

(*c*) The α-bromo-ketone (XII) (13·6 g.), triply distilled before use, was heated in dry carbon tetrachloride (100 ml.) with recrystallised *N*-bromosuccinimide (11 g.) and dibenzoyl peroxide (50 mg.). The mixture was heated for 3 hr., cooled, washed with water, and dried. When

concentrated this yielded crude **4,7-*dibromo*-2,3-*benzocyclohept*-2-*enone***, which was heated for 3 hr. at 100° with collidine (150 ml.), and then briefly at the b. p. After cooling, collidine hydrobromide was filtered off, the filtrate was diluted with chloroform, and the solution was washed with 6N-hydrochloric acid until all collidine had been removed. The tropone was then isolated as described above (yield 5·6 g., 63%). It was possible to purify the crude **4,7-*dibromo*-2,3-*benzocyclohept*-2-*enone*** by distillation at 135—145°/0·003 mm. (with considerable decomposition). The distillate solidified when rubbed with carbon tetrachloride, and crystallised from ethyl acetate; it had m. p. 80° (Found: C, 41·4; H, 3·3; Br, 50·4. $C_{11}H_{10}OBr_2$ requires C, 41·5; H, 3·1; Br, 50·3%). It was stable for *ca.* 3 months at 0°, but at room temperature slowly evolved hydrogen bromide and was converted in 3 months into 2,3-benzotropone hydrobromide (m. p. and mixed m. p. 89°). Like authentic benzotropone hydrobromide, it was decomposed by water to the parent tropone, and yielded 2,3-benzotropone 2,4-dinitrophenylhydrazone (m. p. and mixed m. p.) when treated directly with 2,4-dinitrophenylhydrazine under standard conditions.

Bromination of **2,3-*Benzotropone***.—(*a*) The tropone (V) (100 mg.) was treated with bromine (5 drops). When the initial evolution of hydrogen bromide had subsided, the solution was warmed to complete the reaction. Excess of bromine was then removed under a vacuum; the gummy residue solidified on being rubbed with methanol, yielding **5,7-*dibromo*-2,3-*benzotropone***, m. p. 169° (from ethyl acetate) (Found: C, 42·0; H, 2·3; Br, 50·6. $C_{11}H_8OBr_2$ requires C, 42·0; H, 1·9; Br, 50·95%). Evaporation of the mother-liquors afforded **4,5,7-*tribromo*-2,3-*benzocycloheptа*-2,6-*dienone*** (XVII), m. p. 156° (decomp.) (from ether–pentane) (Found: C, 33·3; H, 1·65. $C_{11}H_7OBr_3$ requires C, 33·2; H, 1·8%), ν(C=O) (Nujol) 1665 cm.$^{-1}$. The substance gave a positive Lassaigne test for bromine, and at its m. p. lost hydrogen bromide, affording the dibromotropone (XVI) described above (m. p. and mixed m. p. 165°).

(*b*) The tropone (600 mg.) in carbon tetrachloride (1 ml.) was treated with bromine (1·25 g.) in carbon tetrachloride (12 ml.), a red crystalline complex separating; this solid redissolved rapidly on warming, or more slowly when the remainder of the bromine solution was added. At no time was any hydrogen bromide evolved. The solvent was removed *in vacuo* at below 30°, leaving a gum which solidified when triturated with methanol–ether. The colourless **4,5,6,7-*tetrabromo*-2,3-*benzocyclohept*-2-*enone*** (XV), crystallised from ethyl acetate–pentane at −30°, had m. p. 123° (Found: C, 28·1; H, 1·55; Br, 67·0. $C_{11}H_8OBr_4$ requires C, 27·9; H, 1·7; Br, 67·1%), ν(C=O) 1700 cm.$^{-1}$.

The red complex dissolved in methanol with loss of colour, and this solution yielded 2,3-benzotropone 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 226°.

When the tetrabromide (XV) was heated at 130° for 5 min., hydrogen bromide was evolved, and the product was identified by m. p. and mixed m. p. and by its infrared spectrum as the dibromotropone (XVI). The same transformation was effected by adding 5N-sodium hydroxide (5 drops) to the tetrabromide (20 mg.) in methanol (2 ml.), the product crystallising.

When the tetrabromide (470 mg.) in ethanol (2 ml.) was heated on the steam-bath for 1 hr. with 0·1N-sodium hydroxide (10 ml., 1 mol.), there separated on cooling **4,5,7-tribromo-2,3-benzocycloheptа-2,6-dienone** (XVII), m. p. and mixed m. p. 152°.

Bromination of Julia's Ketone.—The ketone (100 mg.) was treated with bromine (5 g.) and left at room temperature for 28 days. Excess of bromine was then removed under a vacuum, and the residual gum was heated at 100° for 8 hr. This produced a semisolid material which was triturated with ethyl acetate and crystallised from acetic acid; it then had m. p. 166°, undepressed on admixture with 5,7-dibromo-2,3-benzotropone.

Bromination of Benzosuberenone.—(*a*) The ketone (1 g.) was treated dropwise with bromine until the colour persisted, and thereafter a further 3 g. of bromine was added. The mixture was set aside for 3 days at room temperature, and finally warmed on the steam-bath till the evolution of hydrogen bromide ceased. The gummy residue was titrated with methanol, and the pale yellow **4,7-*dibromo*-2,3-*benzotropone*** (XIX) crystallised from acetic acid, then having m. p. 220° (120 mg.) (Found: C, 41·8; H, 2·3; Br, 50·6. $C_{11}H_8OBr_2$ requires C, 42·0; H, 1·9; Br, 50·95%).

When a few mg. of either of the dibromotropones was boiled in concentrated sulphuric acid for *ca.* 5 min., the solution darkened, but the starting material was recovered on addition of water. It was also recovered from solution in concentrated sulphuric acid after about 4 months at room temperature.

Oxidation of the Dibromobenzotropones.—The dibromo-compound (100 mg.) was heated on

XUM

the steam-bath with potassium permanganate (1 g.) and potassium hydroxide (0·5 g.) in water (10 ml.). After 3 hr. sodium hydrogen sulphite was added to discharge the colour, the solution was filtered, and the filtrate was acidified with 6N-hydrochloric acid and extracted with ether. This afforded a gum which, when heated briefly with acetic anhydride and sublimed at 140—160°/15 mm., had m. p. 130°, undepressed on admixture with phthalic anhydride.

Nitration of 2,3-Benzotropone.—(*a*) The tropone (130 mg.) was added to concentrated sulphuric acid (4 ml.) and nitric acid (1 ml.), and the solution was kept at room temperature for 24 hr. During the first 10 min. the colour changed from yellow to deep magenta, and nitrous fumes were evolved. After 24 hr. the solution (which was once more yellow) was poured on ice. *5,7-Dinitro-2,3-benzotropone*, collected by filtration, washed with water, and crystallised from acetic acid, had m. p. 165° (120 mg.) (Found: C, 53·5; H, 2·6; N, 11·2. $C_{11}H_6O_5N_2$ requires C, 53·7; H, 2·4; N, 11·4%), $\lambda_{max.}$ (log ε) (in 0·1N-NaOH), 220 (4·4), 346 (4·23), 460 (3·32), $\lambda_{min.}$ (log ε) 280 (3·78), 410 (3·26).

The dinitro-compound (45 mg.) was heated on the steam-bath for 2 hr. with 6N-nitric acid (3 ml.), and the mixture was then filtered. Evaporation of the filtrate *in vacuo* gave a small amount of solid which was sublimed, giving needles of phthalic anhydride, m. p. and mixed m. p. 130°.

(*b*) The tropone (0·5 g.) was added to " AnalaR " concentrated nitric acid (15 ml.). The resulting solution slowly evolved brown fumes and deposited crystals. After 5 hr. the latter were filtered off, washed with water, and crystallised from acetic acid; it had m. p. 165° (0·65 g.).

The same product was obtained by using 50% aqueous nitric acid or nitric acid in acetic acid, and in each case nitrous fumes were given off.

(*c*) Dinitrogen tetroxide (prepared by heating a 4 : 1 mixture of " silver sand " and lead nitrate) in a stream of dry nitrogen was passed through a solution of 2,3-benzotropone (100 mg.) in dry carbon disulphide (15 ml.), until the colour changed from yellow to brown and globules of oil began to separate. The solvent was removed at $<30°$ under a vacuum, leaving a brown pasty solid (270 mg.) which decomposed on being ground in Nujol or kept for 15 min. at room temperature. In both cases brown fumes were evolved, and the colour changed to yellow. The product, crystallised from ethyl acetate, had m. p. 164° (212 mg., 96%). It was identical (mixed m. p. and infrared spectrum) with the product above.

Reductions.—(*a*) The dinitro-compound (100 mg.) in acetic acid (25 ml.) was reduced in the presence of platinum (from 100 mg. of platinum oxide). After 1 hr., *ca.* 32 ml. of hydrogen (3·5 mols.) had been absorbed and no further uptake took place. Catalyst and solvent were removed, leaving a pale yellow oil (53 mg.) which was identified as 2,3-benzocyclohept-2-enone (IX) by comparison of infrared spectra and by the identity of the 2,4-dinitrophenylhydrazones.

(*b*) The dinitro-compound (100 mg.) in acetic acid (30 ml.) containing concentrated sulphuric acid (2 ml.) was hydrogenated in presence of platinum (from 110 mg. of platinum oxide). Absorption of hydrogen had practically ceased after 1 hr. when 92 ml. (*ca.* 9 mol.) of hydrogen had been consumed. Catalyst was removed, and the solution was basified with 2N-sodium hydroxide. Continuous ether-extraction failed to isolate any material. The aqueous solution consumed periodate, and after 3 hr. at room temperature with excess of sodium metaperiodate it was extracted with ether. This afforded a trace of oil, from which no solid could be obtained.

In an essentially identical experiment, dry ethanol saturated with hydrogen chloride was used as solvent. Reduction was even more rapid, being complete in 30 min. After removal of catalyst and solvent, there remained a syrup, which was heated under reflux in acetic acid saturated with hydrogen chloride, in an attempt to bring about a hydramine fission.[24] No pure product could be isolated.

The authors are grateful to The Salters' Company for the award of a Scholarship (to D. R. L.), to Drs. J. D. Loudon and J. C. D. Brand for much helpful discussion, and to Mr. J. M. L. Cameron and his staff for the microanalyses.

UNIVERSITY OF GLASGOW. [*Received, April 15th*, 1959.]

[24] Rabe and Schneider, *Annalen*, 1909, **365**, 377.

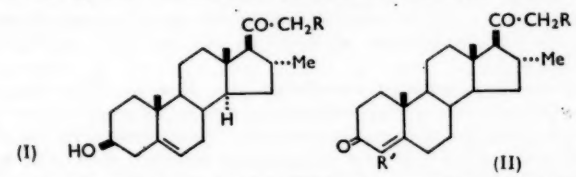
721. *Modified Steroid Hormones. Part XI.** 16α-*Methyldeoxycorticosterone Acetate.*

By Vladimir Petrow and David M. Williamson.

16α-Methyldeoxycorticosterone acetate (II; R = OAc, R′ = H), required for studies of the effect of the 16α-methyl substituent upon mineralocorticoid activity, has been obtained by conventional routes from 3β-hydroxy-16α-methylpregn-5-en-20-one (I; R = H) and 16α-methylprogesterone (II; R = R′ = H).

4-Chloro- (II; R = H, R′ = Cl) and 21-fluoro-16α-methylprogesterone (II; R = F, R′ = H) have also been prepared.

We found previously [1] that 6α-methylation of diverse steroid types often leads to enhancement of progestational, anabolic, and glucocorticoid activity with a concomitant decrease in mineralocorticoid activity, when present. The effect of 6α-methylation in antagonising Na^+ retention and K^+ excretion, however, though marked, is not entirely sufficient to eliminate undesirable water-retaining properties completely from certain steroidal structures. As complete elimination of mineralocorticoid activity accompanies 16α-methoxylation of deoxycorticosterone,[2] it seemed likely that mineralocorticoid activity was highly susceptible to 16α-substitution. We therefore turned our attention to 16α-methylation. Our primary object was to obtain qualitatiye information of the effect of this on the Na^+-retaining and K^+-excreting properties of deoxycorticosterone.†



Bromination of pregnan-20-one derivatives leads normally to 17,21-dibromides. An exception was encountered during the halogenation of 3β-hydroxy-16α-methoxypregn-5-en-20-one,[2] substitution occurring exclusively at position 21. This result was originally ascribed to the deactivating influence of the methoxyl group on the 17-hydrogen atom. Work to be described here and in subsequent publications, however, shows clearly the overriding steric rôle of the 16-substituent in shielding the 17-position from reagent attack with consequential reaction at position 21. Thus, careful bromination of 3β-hydroxy-16α-methylpregn-5-en-20-one (I; R = H) with 2 mols. of bromine led smoothly to the formation of 5,6,21-tribromo-3β-hydroxy-16α-methyl-5α-pregnan-20-one in excellent yield. Treatment with sodium iodide followed by acetolysis gave 21-acetoxy-3β-hydroxy-16α-methylpregn-5-en-20-one (I; R = OAc), which was converted into the required 21-acetoxy-16α-methylpregn-4-ene-3,20-dione (II; R = OAc, R′ = H) by Oppenauer oxidation. The last compound was additionally prepared from 16α-methylprogesterone (II;

* Part X, *J.*, 1959, 788.

† Since completion of the present study, the preparation of 16α-methyl-corticoids has been reported by two separate groups [3] who, like ourselves, have found that in general 16α-methylation decreases mineralocorticoid activity.

[1] (*a*) Burn, Ellis, Petrow, Stuart-Webb, and Williamson, *J.*, 1957, 4092; (*b*) Ackroyd, Adams, Ellis, Petrow, and Stuart-Webb, *ibid.*, p. 4099; (*c*) Grenville, Patel, Petrow, Stuart-Webb, and Williamson, *ibid.*, p. 4105; (*d*) Cooley, Ellis, Kirk, and Petrow, *ibid.*, p. 4112; (*e*) Barton, Ellis, and Petrow, *J.*, 1959, 478.

[2] Cooley, Ellis, and Petrow, *J.*, 1954, 1813.

[3] Arth, Johnston, Fried, Spooncer, Hoff, and Sarett, *J. Amer. Chem. Soc.*, 1958, **80**, 3160; Arth, Fried, Johnston, Hoff, Sarett, Silber, Stoerk, and Winter, *ibid.*, p. 3161; Oliveto, Rausser, Nussbaum, Gebert, Hershberg, Tolksdorf, Eisler, Perlman, and Pechet, *ibid.*, p. 4428; Oliveto, Rausser, Weber, Nussbaum, Gebert, Coniglio, Hershberg, Tolksdorf, Eisler, Perlman, and Pechet, *ibid.*, p. 4431; Taub, Hoffsommer, Slates, and Wendler, *ibid.*, p. 4435; Oliveto, Rausser, Herzog, Hershberg, Tolksdorf, Eisler, Perlman, and Pechet, *ibid.*, p. 6687.

XUM

R = R′ = H) *via* the intermediate 2,21-diethoxalyl derivatives.[4] This was transformed into 2-ethoxalyl-21-iodo-16α-methylpregn-4-ene-3,20-dione by reaction with iodine. Acetolysis followed by removal of the 2-ethoxalyl residue furnished the required ketone (II; R = OAc, R′ = H).

4-Chloro-16α-methylprogesterone (II; R = H, R′ = Cl) was readily obtained by direct chlorination [5] of 16α-methylprogesterone, followed by dehydrohalogenation of the intermediate 4ξ,5ξ-dichloride. The preparation of the 21-chloro-analogue (II; R = Cl, R′ = H), in contrast, proved surprisingly difficult, reaction of 21-ethoxalyl-16α-methylprogesterone [6] with chlorine yielding products which could not be obtained analytically pure. 21-Fluoro-16α-methylprogesterone (II; R = F, R′ = H) was obtained by Oppenauer oxidation of 21-fluoro-16α-methylpregnenolone (I; R = F), readily formed by reaction of the corresponding iodide (I; R = I) with silver fluoride in aqueous acetonitrile.[7]

Experimental

Rotations were determined in a 1 dm. tube for chloroform solutions unless otherwise stated. Ultraviolet absorption spectra (for ethanol solutions) were kindly determined by Mr. M. T. Davies, B.Sc. Alumina (B.D.H. chromatography grade) was used throughout.

5,6,21-Tribromo-3β-hydroxy-16α-methylpregnan-20-one.—Bromine (9·6 g.) in acetic acid (30 ml.) was added dropwise to a stirred suspension of 3β-hydroxy-16α-methylpregn-5-en-20-one (I; R = H) (9·9 g.) in ether (300 ml.) during 30 min. After being stirred for a further 30 min., the mixture was washed with sodium hydrogen carbonate solution and water, and the ether layer was dried (Na_2SO_4). Evaporation under reduced pressure at <30°, followed by crystallisation from methanol, gave *5,6,21-tribromo-3β-hydroxy-16α-methylpregnan-20-one*, needles, m. p. 160—162°, $[\alpha]_D$ +93° (*c* 0·776) (Found: C, 46·2; H, 5·9; Br, 43·3. $C_{22}H_{33}O_2Br_3$ requires C, 46·4; H, 5·8; Br, 42·2%).

21-Iodo-3β-hydroxy-16α-methylpregn-5-en-20-one (I; R = I).—The foregoing tribromide (3·3 g.) in benzene (100 ml.) was treated with sodium iodide (6·6 g.) in absolute alcohol (45 ml.), and the mixture left overnight at room temperature. Water was added and the benzene layer was separated, washed with 3% sodium thiosulphate solution, then with water, and dried. Evaporation of the benzene under reduced pressure at <40° left a residue which crystallised from methanol to give *21-iodo-3β-hydroxy-16α-methylpregn-5-en-20-one*, prisms, m. p. 136—137°, $[\alpha]_D^{21}$ +85° (*c* 0·518) (Found: C, 57·8; H, 7·2; I, 28·3. $C_{22}H_{33}O_2I$ requires C, 57·9; H, 7·3; I, 27·8%).

21-Acetoxy-3β-hydroxy-16α-methylpregn-5-en-20-one (I; R = OAc).—3β-Hydroxy-21-iodo-16α-methylpregn-5-en-20-one (I; R = I) (3 g.) in acetone (30 ml.) was added to potassium hydrogen carbonate (6 g.) and glacial acetic acid (3·8 ml.), and the mixture boiled under reflux for 24 hr. Water was added and the precipitated solids were collected, washed with water, dried, and crystallised from methanol, yielding *21-acetoxy-3β-hydroxy-16α-methylpregn-5-en-20-one*, needles, m. p. 152—154°, $[\alpha]_D^{21}$ +14° (*c* 0·592) (Found: C, 73·9; H, 9·3. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%).

21-Acetoxy-16α-methylpregn-4-ene-3,20-dione (II; R = OAc, R = H).—(*a*) The compound (I; R = OAc) (3 g.) was boiled in cyclohexanone (45 ml.) until 10 ml. of distillate had been collected. Aluminium t-butoxide (3 g.), dissolved in dry toluene (25 ml.), was then added and the mixture heated under reflux for 45 min. Rochelle salt solution was added and the mixture steam-distilled for 6 hr. The product was isolated with ether and crystallised from aqueous methanol, to give *21-acetoxy-16α-methylpregn-4-ene-3,20-dione*, needles, m. p. 136—138°, $[\alpha]_D^{23}$ +160° (*c* 0·706) $\lambda_{max.}$ 240 mμ (ε 16,155) (Found: C, 74·5; H, 8·8; $C_{24}H_{34}O_4$ requires C, 74·5; H, 8·8%).

(*b*) 16α-Methylprogesterone (II; R = R′ = H) (3·3 g.) in t-butyl alcohol (100 ml.) was mixed with ethyl oxalate (11·7 g.) at 70°. When the temperature had fallen to 55°, a solution of sodium methoxide (2·7 g.) in methanol (12 ml.) was added and the mixture stirred for 15 min. To this mixture containing the sodium dienolate of 2,21-diethoxalyl-16α-methylpregn-4-ene-3,20-dione a solution of acetic acid (3 g.) in methanol (160 ml.) was added, followed by iodine

[4] B.P. 775,411.
[5] Kirk, Patel, and Petrow, *J.*, 1956, 1184.
[6] B.P. 738,445.
[7] Jacobsen and Jensen, *Chem. and Ind.*, 1957, 172.

(5·1 g.) in methanol (100 ml.). The mixture was stirred for 2½ hr. at room temperature and the resulting 2,21-diethoxalyl-21-iodo-16α-methylpregn-4-ene-3,20-dione treated with potassium acetate (39 g.) and left at room temperature for 24 hr. The mixture was then poured into ice-water (1 l.) containing sodium thiosulphate (4·5 g.) and concentrated sulphuric acid (6 ml.). The precipitate of 21-acetoxy-2-ethoxalyl-16α-methylprogesterone was collected, washed with water, and dried. It was dissolved in methanol (120 ml.) containing sodium acetate (5 g.) and treated with bromine (2·5 g.) in methanol (25 ml.) at 0°. Sodium methoxide (0·845 g.), in methanol (5 ml.) was then added and the mixture stirred whilst it came to room temperature. Glacial acetic acid (8 ml.) and zinc dust (3·5 g.) were added and the mixture was stirred for 1 hr. The suspended matter was next removed and the filtrate poured into water (1 l.). The precipitate of 21-acetoxy-16α-methylprogesterone was collected, washed with water, and dried. The crude product was chromatographed on alumina (110 g.). Benzene–acetone (9 : 1) eluates gave 21-acetoxy-16α-methylpregn-4-ene-3,20-dione as needles, m. p. and mixed m. p. 134—136° (from methanol). The product gave a purple colour with the tetrazolium reagent.

4-*Chloro*-16α-*methylpregn*-4-*ene*-3,20-*dione* (II; R = H, R′ = Cl).—16α-Methylprogesterone (II; R = R′ = H) (1 g.) in ether (50 ml.) was treated with a 0·84M-solution of chlorine in propionic acid (4·2 ml.) at −30° and left in the dark for 18 hr. at this temperature. More ether was added and the acids were washed out with water. The ether was evaporated under reduced pressure at <30°. The residue crystallised from methanol in needles, m. p. 168—170° (Found: Cl, 16·4. Calc for $C_{22}H_{32}O_2Cl_2$: Cl, 17·8%). This crude 4ξ,5ξ-dichloride (250 mg.) was dissolved in benzene (3 ml.) containing pyridine (0·5 ml.) and left at room temperature for 4 hr. The product was isolated with ether and crystallised from methanol, to give 4-*chloro*-16α-*methylpregn*-4-*ene*-3,20-*dione*, needles, m. p. 180—182°, $[\alpha]_D^{22}$ +175° (*c* 1·148), $\lambda_{max.}$ 254—256 mμ, (ε 13,900) (Found: C, 72·9; H, 8·7; Cl, 9·8. $C_{22}H_{31}O_2Cl$ requires C, 72·8; H, 8·5; Cl, 9·8%).

21-*Chloro*-16α-*methylpregn*-4-*ene*-3,20-*dione* (II; R = Cl, R′ = H).—16α-Methylprogesterone (3·3 g.) in dry benzene (75 ml.) was added rapidly to a mixture of dry sodium methoxide (0·59 g.), dry benzene (20 ml.), and ethyl oxalate (2·7 ml.) which had been stirred at room temperature until a clear solution was obtained and had then been diluted with absolute alcohol (1 ml.). After being stirred at room temperature for 2 hr., the mixture was diluted with dry ether (250 ml.) and after a further 45 minutes' stirring the precipitated sodium enolate of 21-ethoxalyl-16α-methylpregn-4-ene-3,20-dione was collected and dried. It was dissolved in methanol (100 ml.) and treated dropwise with a solution of chlorine in dimethylformamide (45 ml.) containing 0·027 g. of chlorine/ml., during 1 hr. at −20°. The mixture was stirred at this temperature for a further 60 min., then treated with 3·4N-methanolic sodium methoxide (4·8 ml.) at 0° for 1 hr. A saturated salt solution was then added and the product isolated with benzene and chromatographed on alumina. Benzene eluates gave slightly impure 21-chloro-16α-methylpregn-4-ene-3,20-dione which crystallised from methanol in needles, m. p. 178—180°, $[\alpha]_D^{24}$ +171° (*c* 0·498) $\lambda_{max.}$ 243 mμ (ε 14,350) (Found: C, 71·9; H, 8·5; Cl, 10·4. Calc. for $C_{22}H_{31}O_2Cl$: C, 72·8; H, 8·5; Cl, 9·8%).

21-*Fluoro*-3β-*hydroxy*-16α-*methylpregn*-5-*en*-20-*one* (I; R = F).—To 3β-hydroxy-21-iodo-16α-methylpregn-5-en-20-one (I; R = I) (1·6 g.) in acetonitrile (50 ml.) were added aqueous silver fluoride solution (50% w/v) (5 ml.) and sufficient distilled water to give a clear solution. The whole was kept at 50° for 40 hr., then filtered, and water was added to the filtrate. The precipitate was collected and crystallised from methanol, to give 21-*fluoro*-3β-*hydroxy*-16α-*methylpregn*-5-*en*-20-*one*, prisms, m. p. 190—192°, $[\alpha]_D^{20}$ +10° (*c* 0·514) (Found: C, 75·5; H, 9·4. $C_{22}H_{33}O_2F$ requires C, 75·8; H, 9·5.

21-*Fluoro*-16α-*methylpregn*-4-*ene*-3,20-*dione* (II; R = F, R′ = H).—Oxidation of compound (I; R = F) (0·9 g.) in cyclohexanone (12 ml.) with aluminium t-butoxide (1·0 g.) in toluene (8 ml.) for 45 min. under reflux, followed by steam-distillation in the presence of Rochelle salt solution, gave an oil which was isolated with chloroform. Crystallisation from acetone–hexane gave 21-*fluoro*-16α-*methylpregn*-4-*ene*-3,20-*dione*, prisms, m. p. 139—140°, $[\alpha]_D^{23}$ +177° (*c* 0·34) $\lambda_{max.}$ 240 mμ (ε 16,350) (Found: C, 76·4; H, 9·2; F, 5·1. $C_{22}H_{31}O_2F$ requires C, 76·2; H, 8·9; F, 5·5%).

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish this work.

CHEMICAL RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES LTD., LONDON, N.1.

[*Received, June 3rd,* 1959.]

XUM

722. *The Chemistry of Fungi. Part XXXVII.*[1] *The Structure of Rubropunctatin.*

By E. J. Haws, J. S. E. Holker, A. Kelly, A. D. G. Powell, and Alexander Robertson.

A new pigment, $C_{21}H_{22}O_5$, rubropunctatin has been isolated from *Monascus rubropunctatus* Sâto. With aqueous ammonia this gives a nitrogen analogue, rubropunctatamine, $C_{21}H_{23}O_4N$, which, on reduction with zinc and acetic acid is degraded to an 8-hydroxyisoquinoline derivative, aporubropunctatamine, $C_{20}H_{25}O_2N$, and one mol. of carbon dioxide. From degradative studies on the parent compound and these derivatives, aporubropunctatamine is shown to have structure (XII), whilst structures (XIXa) and (XVIII) are proposed for rubropunctatin and rubropunctatamine respectively.

Exhaustive hydrogenation of rubropunctatin gives hexahydroaporubropunctatin, $C_{20}H_{30}O_3$, for which structure (XXIa) is proposed.

The probable biogenesis of rubropunctatin is discussed and possible structural implications for the related compound rotiorin are tentatively suggested.

During an investigation into the metabolic products of the *Monascus* genus in this Department, a new red pigment, rubropunctatin was isolated from the mycelium of *M. rubropunctatus* Sâto. In a preliminary account of this work [2] a close relation was pointed out between the properties of the pigments sclerotiorin,[1,3,4,5,6] rotiorin,[7] monascin,[8] monascorubrin,[9] and rubropunctatin.

The present paper describes the structural investigations on rubropunctatin which have been carried out during the last five years.

Rubropunctatin has the molecular formula, $C_{21}H_{22}O_5$, although the formula, $C_{22}H_{24}O_5$, cannot be excluded by analysis alone and the latter was originally suggested.[2] This compound, which has a very high negative specific rotation, contains no hydroxyl (Zerewitinoff) and no methoxyl group. The ultraviolet [$\lambda_{max.}$ 218, 246, 290, and 460 mμ (log ε 4·17, 4·09, 3·98, and 4·30)] and infrared spectra [$\nu_{max.}$ 1757, 1724, 1656, 1636, and 1577 cm.$^{-1}$ (mull)] together indicated the presence of a highly conjugated chromophore containing carbonyl functions. The pigment was extracted from ethereal solution by dilute aqueous sodium hydroxide and was precipitated unchanged on immediate treatment of the alkaline solution with mineral acid. This, in conjunction with the absence of active hydrogen, suggested that the compound contains a potentially acidic function. Prolonged treatment with sodium hydroxide decomposed the pigment to a complex unresolved mixture of acidic products. The isolation of hexanoic acid by degradation of rubropunctatin with alkali [2] has not been substantiated. The pigment was not reduced by alkaline sodium dithionite in alcohol or by sulphur dioxide, and so does not contain a quinone system. Although there was an obvious reaction with 2,4-dinitrophenylhydrazine hydrochloride, a crystalline derivative could not be isolated.

Hydrogenation of rubropunctatin was extremely complex and will be discussed in detail below, but under very mild conditions in the presence of palladium on barium sulphate a dihydro-derivative was isolated. However, the conditions for this reaction appeared to be critical and difficultly reproducible.

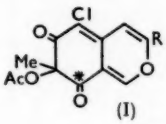
[1] Part XXXVI, Dean, Staunton, and Whalley, *J.*, 1959, 3004.
[2] Powell, Robertson, and Whalley, *Chem. Soc. Special Publ.*, 1957, No. 5, p. 27.
[3] Eade, Page, Robertson, Turner, and Whalley, *J.*, 1957, 4913.
[4] Graham, Page, Robertson, Travers, Turner, and Whalley, *J.*, 1957, 4924.
[5] Fielding, Graham, Robertson, Travers, and Whalley, *J.*, 1957, 4931.
[6] Fielding, Robertson, Travers, and Whalley, *J.*, 1958, 1814.
[7] Jackmann, Robertson, Travers, and Whalley, *J.*, 1958, 1825.
[8] Salvman and Karrer, *Helv. Chim. Acta*, 1932, **15**, 18; Geiger and Karrer, *Helv. Chim. Acta*, 1941, **24**, 289.
[9] Nishikawa, *J. Agric. Chem. Soc. Japan*, 1932, **8**, 1007.

On ozonolysis, rubropunctatin gave acetaldehyde which was isolated as the 2,4-dinitrophenylhydrazone. Although no other pure product could be isolated from this reaction, the result indicated the presence of an ethylidene group in the pigment. Oxidation of rubropunctatin with alkaline hydrogen peroxide or chromic oxide gave hexanoic acid, characterised as the *p*-bromophenacyl ester and as the piperazine salt, showing that the pigment contains an n-pentyl side-chain. Thus, of the three *C*-methyl groups shown to be present in the compound by Kuhn–Roth estimation, two are in ethylidene and n-pentyl side-chains.

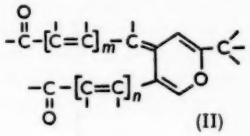
With dilute aqueous ammonia at room temperature rubropunctatin rapidly formed the violet compound, rubropunctatamine, $C_{21}H_{23}O_4N$. Dihydrorubropunctatamine was prepared by reaction of dihydrorubropunctatin with ammonia, and by hydrogenation of rubropunctatamine. With methylamine under similar conditions rubropunctatin gave *N*-methylrubropunctatamine. These nitrogen analogues are feebly basic, forming yellow hydrochlorides in concentrated hydrochloric acid, whence the parent bases are regenerated by dilution with water. Alcoholic suspensions of rubropunctatamine and its dihydro-derivative dissolved immediately on addition of 2N-sodium hydroxide but the *N*-methyl derivative was insoluble, showing that only the two former compounds are acidic. The extremely mild conditions under which the nitrogen analogues are formed by apparent replacement of O by NH or NMe and the properties of these compounds are analogous to the formation and properties of the corresponding derivatives of sclerotiorin [1,3] (Ia). A further similarity was the oxidation of rubropunctatamine by nitric acid to pyridine-2,4,5-tricarboxylic acid, which had been isolated on similar oxidation of sclerotioramine [6] and rotioramine.[7] It therefore seemed likely that rubropunctatin contained the same

(a) R = ·CH:CH·C(Me):CH·CHMeEt

(b) R = ·CH$_2$·CH$_2$·CH(Me)·CH$_2$·CHMeEt



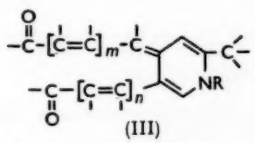
(I)



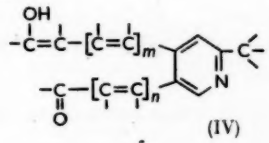
(II)

(a) R = H

(b) R = Me



(III)



(IV)

chromophoric system as sclerotiorin, or a closely related system of type (II), in which the replaceable oxygen function is independently conjugated with two carbonyl functions. On this basis rubropunctatamine would contain a chromophoric system of type (IIIa) and *N*-methylrubropunctatamine would contain system (IIIb). Accordingly the solubility of rubropunctatin and rubropunctatamine in alkali can be attributed respectively to a vinylogous lactone system and to an enolic hydroxyl group generated by amide-imine tautomerism of type (IIIa) $\rightleftharpoons$ (IV).

Rubropunctatamine with alkaline potassium permanganate and with ozone gave hexanoic acid and acetaldehyde respectively, establishing that the pentyl and the ethylidene side-chains of rubropunctatin are present in rubropunctatamine. Ozonolysis of dihydrorubropunctatamine did not produce acetaldehyde, so it is the double bond of the ethylidene group that is hydrogenated.

Reduction of rubropunctatamine with zinc and acetic acid gave one mol. of carbon dioxide and a colourless optically inactive compound, $C_{20}H_{25}O_2N$, aporubropunctatamine. This formed a dihydro-derivative, identical with the product obtained by reduction of dihydrorubropunctatamine with zinc and acetic acid. Similar reduction of *N*-methylrubropunctatamine gave the red compound *N*-methylaporubropunctatamine, $C_{21}H_{27}O_2N$. Although, as pointed out previously, it was impossible to differentiate between C_{21} and

XUM

C_{22} formulations for rubropunctatin and its nitrogen analogue on the basis of analytical determinations alone, elemental analyses for aporubropunctatamine and many derivatives establish the C_{20} formulation for this compound, and since in its formation from rubropunctatamine only one carbon atom appears to be extruded as carbon dioxide, the C_{21} rather than C_{22} formulation is preferred for the latter compound and hence for rubropunctatin.

Aporubropunctatamine is soluble in alkali, has an infrared band at 3120 cm.$^{-1}$, and gives an alkali-insoluble monoacetate: it thus contains a phenolic hydroxyl group. The infrared spectrum of the acetate was devoid of absorption in the 3 μ region and had a strong band at 1757 cm.$^{-1}$ due to a phenolic acetate group. Similarly, aporubropunctatamine with methyl iodide and potassium carbonate in acetone gave an *O*-methyl derivative in low yield, *O*-methylation rather than *N*-methylation being assumed on the basis of (*a*) the great similarity between the ultraviolet spectra of this derivative and the *O*-acetate,

FIG. 1. FIG. 2.

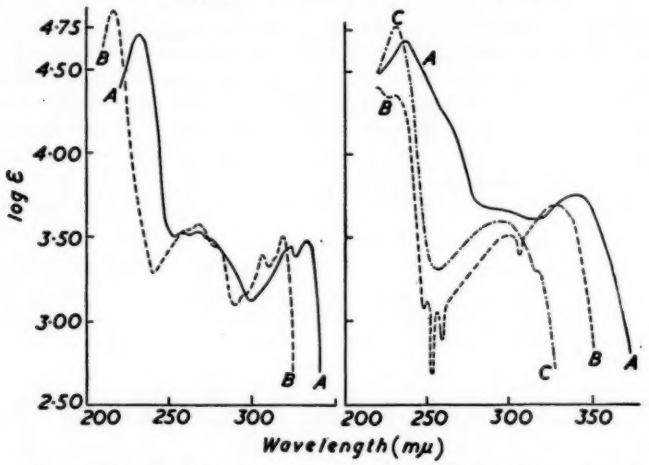


FIG. 1. *Absorption spectra of* (*A*) O-*acetyldihydroaporubropunctatamine, and* (*B*) *isoquinoline in* 95% *alcohol.*

FIG. 2. *Absorption spectra of* (*A*) *dihydroaporubropunctatamine and* (*B*) 8-*hydroxy-, and* (*C*) 6-*hydroxy-isoquinoline in* 95% *alcohol.*

(*b*) the quantitative yield of methyl iodide in the Zeisel determination, and (*c*) non-identity with *N*-methylaporubropunctatamine. The second oxygen function in aporubropunctatamine is ketonic, as *O*-methylaporubropunctatamine formed an oxime and reduction of aporubropunctatamine and its dihydro-derivative with potassium borohydride gave monohydric alcohols which formed diacetates showing infrared bands at 1735 (alcoholic acetate) and 1773 cm.$^{-1}$ (phenolic acetate). Borohydride reduction of *O*-methylaporubropunctatamine similarly gave a monohydric alcohol which formed a monoacetate showing an infrared band at 1735 cm.$^{-1}$. The ketonic carbonyl group in aporubropunctatamine appeared to be isolated from the main chromophore since the compound showed an infrared band at 1704 cm.$^{-1}$ and the ultraviolet spectrum of the borohydride reduction product from aporubropunctatamine showed no shift of absorption bands when compared with the spectrum of the parent ketone.

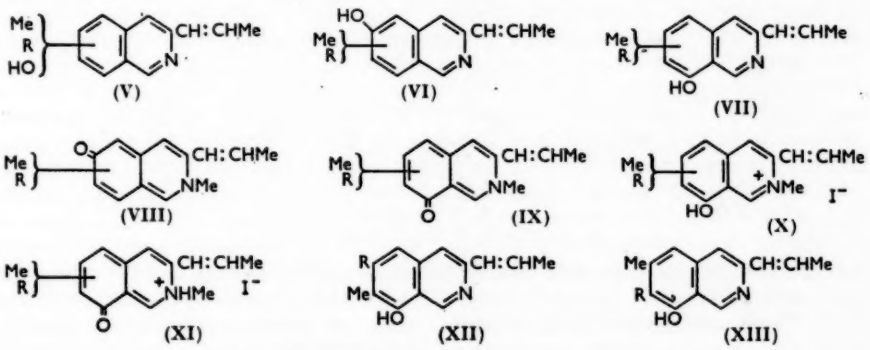
The presence of a propenyl group in aporubropunctatamine was demonstrated by ozonolysis of the *O*-acetyl derivative, acetaldehyde and the bisnor-acid $C_{20}H_{23}O_5N$ being produced. This propenyl group appeared to be conjugated with the main chromophoric system since the ultraviolet absorption bands of dihydroaporubropunctatamine and its

acetate were at 20 mμ lower wavelength than the corresponding bands of aporubropunctatamine and its acetate respectively.

The ultraviolet absorption spectra of *O*-acetyldihydroaporubropunctatamine and the diacetate of its borohydride reduction product were identical and similar to the spectrum of isoquinoline in intensity and relative position of the absorption bands (Fig. 1) but, as in the case of aposclerotioramine [5] and aporotioramine,[7] were at wavelengths longer by about 20 mμ. Since acetoxyl groups do not influence the ultraviolet absorption of aromatic systems [10] and the conjugation of the propenyl side-chain has been removed in the dihydro-derivatives, these spectra provide reasonable evidence regarding the isoquinoline nature of the nucleus in the apo-compounds. On the assumption that no skeletal rearrangement occurs in the formation of the apo-compounds from rubropunctatamine, the production of pyridine-2,4,5-tricarboxylic acid by oxidation of the latter compound supports this hypothesis and, further, indicates that the isoquinoline nucleus has a substituent in the 3-position. This substituent is the propenyl group since the ozonolysis acid from *O*-acetylaporubropunctatamine gave an intense red colour in alcohol with ferrous sulphate, a reaction which is characteristic of a carboxyl group in the *ortho*-position to an aromatic nitrogen atom.[11]

The nature of the remaining substituent groups in the isoquinoline skeleton of the apo-compounds can now be completely defined. The 3-propenylisoquinoline moiety accounts for twelve of the twenty carbon atoms in aporubropunctatamine, and as the pentyl side-chain would hardly be affected in the formation of the apo-compound from rubropunctatamine, this accounts for a further five. Of the remaining three carbon atoms, one is present in an isolated keto-group and a second must be in a methyl group to account for the observed *C*-methyl content of the apo-compounds. On this basis, aporubropunctatamine must contain either an acetonyl group together with a pentyl side-chain, or a methyl group together with a β-oxoheptyl group. The former possibility was excluded since aporubropunctatamine gave a negative iodoform test. Hence, this compound has the partial structure (V), in which the substituent groups are attached directly to the benzene ring of the isoquinoline skeleton.

The orientation of these substituents was established as follows. Aporubropunctatamine gave a methiodide, $C_{21}H_{27}O_2NI$, which generated *N*-methylaporubropunctatamine on treatment with sodium carbonate. This reaction, which contrasts with the formation



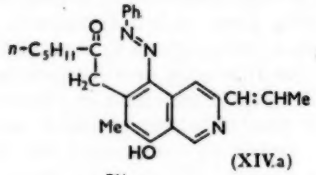
R = *n*-C_5H_{11}·CO·CH_2–

of an *O*-methyl ether described above, has parallels in the aposclerotioramine [5] and aporotioramine [7] series, and indicated that the phenolic hydroxyl group of aporubropunctatamine must be in a position which would permit amide-enol tautomerism, *i.e.*, the group

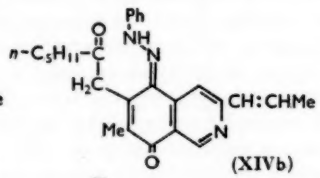
[10] Cooke, Macbeth, and Winzor, *J.*, 1939, 878.
[11] Ley, Schwarte, and Münnich, *Ber.*, 1924, **57**, 349.

must be at the 6- or 8-position of the isoquinoline nucleus, thus leading to the partial structures (VI) or (VII) for aporubropunctatamine, and (VIII) or (IX) for its *N*-methyl derivative. The methiodide could thus be regarded as (X) or a tautomeric *N*-methyl hydriodide (XI) (or equivalent structures derived from 6-hydroxyisoquinoline). A study of the ultraviolet spectrum of dihydroaporubropunctatamine (which is devoid of a side-chain conjugated with the nucleus) suggested an 8- in preference to a 6-hydroxyisoquinoline nucleus. Thus, Fig. 2 shows that the absorption bands in this spectrum are much more similar in intensity and relative position to the corresponding bands of 8- than to those of 6-hydroxyisoquinoline, except that the bands in the spectrum of the apo-compound are at about 20 mμ longer wavelengths than in 8-hydroxyisoquinoline owing to the bathochromic effects of the substituents. Further, aporubropunctatamine gave a blue colour ($\lambda_{max.}$ 650 mμ) with 2,6-dichlorobenzoquinone chlorimide under the conditions of King, King, and Manning,[12] indicating the presence of an unsubstituted position *para* to the phenolic hydroxyl group, *i.e.*, an 8-hydroxyisoquinoline group unsubstituted in the 5-position. Thus, aporubropunctatamine appeared to have structure (XII) or (XIII). Finally, this compound did not form an anhydro-compound when heated and therefore appeared not to contain a phenolic hydroxyl group in the *ortho*-position to the β-oxoheptyl side-chain. Thus, structure (XII) is preferred to structure (XIII) for aporubropunctatamine.

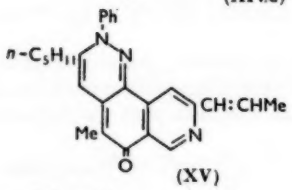
Confirmation was provided as follows. The potassium borohydride reduction product



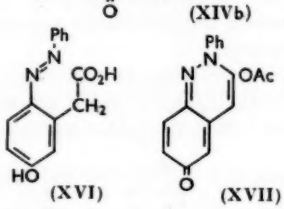
(XIVa)



(XIVb)

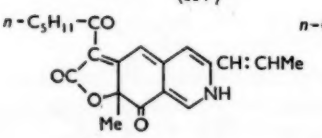


(XV)

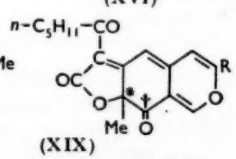


(XVI)

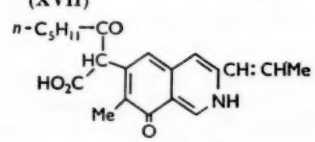
(XVII)



(XVIII)



(XIX)
(a) R = CH:CHMe
(b) R = $CH_2 \cdot CH_2Me$



(XX)

from aporubropunctatamine with benzenediazonium chloride gave an azo-dye $C_{26}H_{31}O_2N_3$ which gave an intensely coloured sodium salt with dilute sodium hydroxide. It is well known [13] that compounds with an azo-group in the *ortho*-position to a phenolic hydroxyl group, *e.g.*, 1-azo-2-naphthol, are insoluble in dilute alkali owing to hydrogen-bonding. Thus, with the apo-derivative, coupling has occurred in the *para*-position to the phenolic hydroxyl group, supporting the assumption that the *apo*-compounds contain an unsubstituted position *para* to the phenolic hydroxyl group.

Aporubropunctatamine with benzenediazonium chloride gave an alkali-insoluble red

[12] King, King, and Manning, *J.*, 1957, 563.
[13] Saunders, " The Aromatic Diazo Compounds," Arnold and Co., London, 1949, p. 198.

product, $C_{28}H_{27}ON_3$, containing a molecule of water less than the expected structure (XIVa). The infrared spectrum of this compound showed no absorption which could be attributed to either hydroxyl or isolated keto-groups and it was therefore assumed that the initially formed coupling product (XIVa $\rightleftharpoons$ XIVb) underwent spontaneous intramolecular condensation to give the cinnoline derivative (XV). Although this type of cyclisation does not appear to have been reported previously, compounds of type (XVI) are cyclised [14] by acetic anhydride and sulphuric acid to cinnoline derivatives (XVII). The difference in ease of cyclisation of the ketone (XIV) and the carboxylic acid (XVI) is probably due to the greater reactivity of the keto-group towards nucleophiles. The cyclisation is being investigated further. If the cinnoline structure is correct, it confirms structure (XII) for aporubropunctatamine.

Provided that no molecular rearrangement occurs in the reductive aromatisation of rubropunctatamine to aporubropunctatamine and a mol. of carbon dioxide, the derivation of a complete structure for rubropunctatamine requires formal replacement of two hydrogen atoms by carbon dioxide. The structure derived for rubropunctatamine must explain the ease of aromatisation and contain a chromophore of type (II). Structure (XVIII) for rubropunctatamine and hence (XIXa) for rubropunctatin most adequately fulfil these conditions. The γ-lactone ring is theoretically derived from a γ-hydroxy-acid in which the alcoholic hydroxyl group is flanked by both a double bond and a carbonyl group. By analogy with the well-known reductive fission of α-ketol esters and allylic esters, similar fission of rubropunctatamine would be expected to occur readily with formation of an intermediate β-keto-acid (XX), which on decarboxylation and prototropic shift would afford aporubropunctatamine (XII). Further, the asymmetric carbon atom marked * in structure (XIXa) explains the optical activity of rubropunctatin. Although the intense colour of rubropunctatamine prevented determination of optical activity, it seems unlikely that the mild conditions used in the formation of this nitrogen analogue would destroy or racemise the asymmetric centre. Consequently it is assumed that rubropunctatamine contains an asymmetric centre which is destroyed in the formation of the apo-compounds. This hypothesis is fully accommodated in structures (XVIII) and (XII).

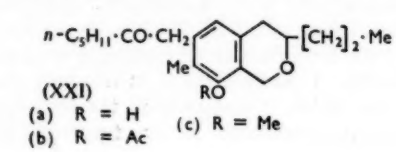
The infrared spectra of rubropunctatin and rubropunctatamine seem to be compatible with structures (XIXa) and (XVIII) respectively. On conversion of rubropunctatin into rubropunctatamine the principal absorption bands in the carbonyl stretching region all undergo bathochromic shifts. This is qualitatively analogous to the shift of carbonyl frequency on conversion of an ester into an amide, and indicates that all three carbonyl functions of rubropunctatin are conjugated with the ethereal oxygen atom, in agreement with structure (XIXa). Despite the difficulty of detailed spectral analysis in highly conjugated systems, the 1757 cm.$^{-1}$ band in the spectrum of rubropunctatin can be tentatively ascribed to the $\alpha\beta$-unsaturated γ-lactone, the 1656 cm.$^{-1}$ band to a highly conjugated ketonic carbonyl group, and the bands at 1636 and 1575 cm.$^{-1}$ to conjugated double bonds. The absorption at 1724 cm.$^{-1}$ in the spectrum of rubropunctatin seems anomalous at first sight. However, a similar band at 1715 cm.$^{-1}$ (in $CHCl_3$) in the spectrum of sclerotiorin has been ascribed to the carbonyl group marked * in formula (Ia), the abnormally short wavelength being attributed to strain in the region of this group.[1] Similar arguments can be applied to structure (XIXa) for rubropunctatin and indicate that the band at 1724 cm.$^{-1}$ is due to the carbonyl group marked †.

The interpretation of ultraviolet spectra in cross-conjugated systems as complex as that in rubropunctatin is extremely difficult. Even when the influence of the propenyl system is removed in the dihydro-derivative (XIXb), cross-conjugation still exists between the γ-lactone and the hexanoyl group. In the absence of detailed correlation it is interesting that the ultraviolet spectra show the chromophoric system of dihydrorubropunctatin

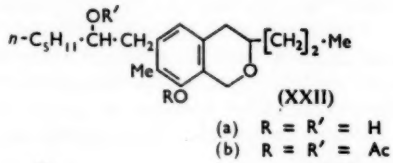
[14] Kornfeld, *J. Amer. Chem. Soc.*, 1948, **70**, 1373.

(XIXb) [$\lambda_{max.}$ 218 and 400 mμ (log ε 4·22 and 4·40)] to be more extensively conjugated than that of tetrahydrosclerotiorin (Ib) [$\lambda_{max.}$ 225 and 343 mμ (log ε 4·13 and 4·30)], in agreement with the proposed formulæ.

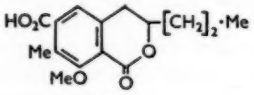
Exhaustive hydrogenation of rubropunctatin involved uptake of 5—6 mols. of hydrogen and was accompanied by remarkable fluorescent colour changes. Great difficulty was experienced in the isolation of a pure compound but, under controlled conditions, 10% of a compound $C_{20}H_{30}O_3$ was isolated which is though to be hexahydroaporubropunctatin (XXIa) for the following reasons. (1) The infrared spectrum showed bands at 3663 (phenolic OH), 1718 (isolated C=O), and 1626 cm.$^{-1}$ (aromatic). (2) The compound gave a monoacetate (XXIb) and a monomethyl ether (XXIc). (3) Hexahydroaporubropunctatin, like aporubropunctatamine, gave a blue colour with Gibb's reagent, indicating an unsubstituted position *para* to the phenolic hydroxyl group. (4) The presence of a keto-group was established by the formation of an oxime from hexahydro-*O*-methylaporubropunctatin and by reduction of the phenol with potassium borohydride to the monohydric alcohol (XXIIa) which formed a diacetate (XXIIb). (5) Hexahydro-*O*-methylaporubropunctatin with potassium permanganate gave a carboxylic acid, $C_{15}H_{18}O_5$. Although insufficient of the acid has been obtained for characterisation, it probably has structure (XXIII), arising by oxidation of the hexanoyl side-chain and the benzyl ether system. A direct analogy for the oxidation of a similar benzyl ether system to a lactone is conversion of methyl dihydro-*O*-dimethylcitrinin (XXIV) into methyl dihydro-*O*-dimethylcitrinone (XXV) by chromic oxide or potassium permanganate.[15] Further, the infrared spectrum of the acid (XXIII) shows bands at 2646 and 1698 cm.$^{-1}$ (aryl acid) and 1718 cm.$^{-1}$ (δ-lactone of aryl acid).



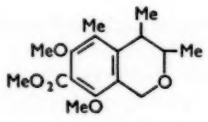
(XXI)
(a) R = H
(b) R = Ac
(c) R = Me



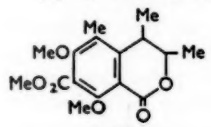
(XXII)
(a) R = R′ = H
(b) R = R′ = Ac



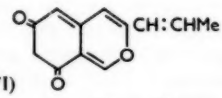
(XXIII)



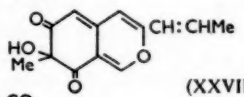
(XXIV)



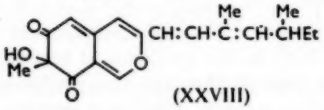
(XXV)



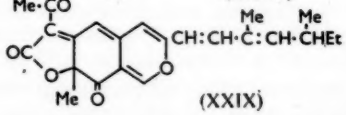
(XXVI)



(XXVII)



(XXVIII)



(XXIX)

At first sight it appears that rubropunctatin (XIXa) must be derived biogenetically from an unusual branched sequence of acetate units. However, an intermediate of type (XXVI) is probably first formed from a linear sequence of six acetate units, and this, on methylation from the C_1 pool and hydroxylation, would give an intermediate (XXVII). Acylation of the tertiary hydroxyl group with 3-oxo-octanoic acid, derived from a linear sequence of four acetate units, followed by aldol condensation and dehydration, would give rubropunctatin. This pattern of biogenesis is similar to that postulated for sclerotiorin

[15] Brown, Robertson, and Whalley, *J.*, 1949, 867.

on the basis of labelled acetate studies,[16] where an intermediate of type (XXVIII) is apparently formed from a linear sequence of eight acetate units. Further, since rotiorin [7] is a co-pigment of sclerotiorin in *Penicillium sclerotiorum* van Beyma, it seems likely that it has structure (XXIX), derived from an intermediate of type (XXVIII) by acetoacetylation of the tertiary hydroxyl group and subsequent aldol condensation and dehydration. We have been informed by Dr. W. B. Whalley and his associates of this Department that structure (XXIX) for rotiorin is in better agreement with recent experimental findings than the structure recently suggested.[7]

Experimental

Unless otherwise stated, ultraviolet absorption spectra were measured for 95% alcohol solutions with a Unicam S.P. 500 spectrophotometer, infrared spectra for mineral oil dispersions with a Perkin–Elmer Model 21 instrument, and optical rotations for chloroform solutions.

Rubropunctatin and Monascin from Monascus rubropunctatus *Sâto.*—A culture of this organism, obtained from the Centraal-bureau voor Schimmelcultures, Baarn, Holland, was grown on Czapek–Dox solution (prepared according to Raistrick and Rintoul [17]) at 30° for 14—20 days until pigmentation was complete. The red mycelial mats were dried in air at room temperature, milled, and percolated successively with light petroleum (b. p. 60—80°) and ether. The former extract was concentrated and the crude pigment which separated was resolved by fractional crystallisation from ether into *rubropunctatin* (XIXa), orange needles, m. p. 156·5—157° (decomp.) (from ether or alcohol), $[\alpha]_D$ −3481 (*c* 1·07), $\lambda_{max.}$ 218, 246, 290, and 460 mμ (log ε 4·17, 4·09, 3·98, and 4·30), $\nu_{max.}$ 1757s, 1724s, 1656s, 1636s, and 1577s cm.$^{-1}$ [Found: C, 71·1, 71·2, 71·6; H, 6·3, 6·3, 6·5; *C*-Me, 11·1%; OMe, 0·0; active H, 0·0; *M* (Menzies–Wright), 369. $C_{21}H_{22}O_5$ requires C, 71·2; H, 6·3; 3*C*-Me, 12·7%; *M*, 354·4], and monascin, yellow plates, m. p. 142—144° (decomp.) (from ether), $[\alpha]_D$ +544° (*c* 1·27) [Found: C, 70·6, 70·1; H, 7·5, 7·5%; active H, 0·0; *M* (*X*-ray), 348. Calc. for $C_{21}H_{26}O_5$: C, 70·4; H, 7·3%; *M*, 358]. On concentration, the ether extract from the mycelium gave a further amount of rubropunctatin, uncontaminated with monascin. The yields of pigments from the mycelium were variable, 440 penicillin flasks, each containing 500 ml. of culture medium, producing up to 26 g. of rubropunctatin and up to 4 g. of monascin.

Rubropunctatin was soluble in the usual organic solvents but only sparingly soluble in light petroleum and carbon tetrachloride. Although insoluble in cold 2N-sodium hydroxide, the compound was extracted from solution in ether by 2N-sodium hydroxide to give an intensely violet solution, from which it was recovered unchanged by immediate acidification. Solutions of the pigment in alcohol were not decolorised by sodium dithionite and sodium hydroxide or by sulphur dioxide.

Rubropunctatin was extensively degraded by treatment with saturated aqueous barium hydroxide at 100° for 5 hr. or 5% sodium hydroxide in alcohol under reflux for 1 hr. Acidification and distillation in steam of the resultant hydrolysates gave mixtures of volatile acidic products which have not been separated.

Dihydrorubropunctatin (XIXb).—Hydrogenation of rubropunctatin (0·5 g.) suspended in ether (100 ml.) with hydrogen (approx. 2 mols. absorbed) at atmospheric pressure and 5% palladium–barium sulphate (500 mg.) was complete in 2 hr. The filtered solution was diluted with light petroleum (b. p. 40—60°) (15 ml.) and concentrated until crystallisation commenced. *Dihydrorubropunctatin* (292 mg.) was obtained as yellow needles, m. p. 118—119° [after repeated recrystallisation from light petroleum (b. p. 40—60°)], $[\alpha]_D$ −2474° (*c* 1·03), $\lambda_{max.}$ in cyclohexane 218 and 400 mμ (log ε 4·22 and 4·40) (Found: C, 70·9; H, 6·7. $C_{21}H_{24}O_5$ requires C, 70·8; H, 6·8%).

Ozonolysis of Rubropunctatin.—A stream of ozone and oxygen was led into a solution of rubropunctatin (1 g.) in acetic acid (50 ml.) until absorption was complete (*ca.* 2·5 hr.). The orange solution was poured into water (1 l.) containing zinc dust (3 g.), and 12 hr. later the insoluble brown amorphous residue and excess of zinc were collected. Acetaldehyde was removed from the aqueous filtrate by steam and characterised as the 2,4-dinitrophenylhydrazone derivative (308 mg., 51%), yellow blades (from alcohol), m. p. and mixed m. p. 164—166° (Found: C, 42·6; H, 3·6; N, 24·9. Calc. for $C_8H_8O_4N_4$: C, 42·9; H, 3·6; N, 25·0%).

[16] Birch, Fitton, Pride, Ryan, Smith, and Whalley, *J.*, 1958, 4576.
[17] Raistrick and Rintoul, *Phil. Trans.*, 1931, *B*, **220**, 2.

XUM

Oxidation of Rubropunctatin.—(a) *With alkaline hydrogen peroxide.* Rubropunctatin (1 g.) in N-alcoholic sodium hydroxide (30 ml.) containing water (1·2 ml.) and 30% hydrogen peroxide (8 ml.) was kept at room temperature for 5 days during which the colour changed from deep purple to bright yellow (24 hr.) and then faded (4 days). The mixture was diluted with water (60 ml.) and acidified with hydrochloric acid, and excess of hydrogen peroxide was removed with sulphur dioxide. After isolation by continuous extraction with ether, the products were partially separated by distillation in steam, giving an intractable non-volatile residue (357 mg.) and a volatile oil (213 mg.) (isolated from the distillate with ether) from which hexanoic acid was characterised as the *p*-bromophenacyl ester, plates (from aqueous alcohol), m. p. and mixed m. p. 71—72° (Found: C, 53·9; H, 5·6. Calc. for $C_{14}H_{17}O_3Br$: C, 53·7; H, 5·5%), and as the piperazine salt, needles (from dioxan), m. p. and mixed m. p. 109° (Found: C, 59·9; H, 10·4; N, 8·6. Calc. for $C_{16}H_{34}O_4N_2$: C, 60·3; H, 10·8; N, 8·8%).

(b) *With chromic acid.* To a solution of rubropunctatin (500 mg.) in acetic acid (10 ml.) was added portionwise during 24 hr. a N-solution of chromic acid in acetic acid (50 ml.). After treatment with a few drops of methanol, the solvent was removed *in vacuo*, and the residue was shaken with concentrated hydrochloric acid (1 ml.) in water (100 ml.). Hexanoic acid (58 mg.) was separated in steam, isolated in ether, and characterised as the piperazine salt, needles (from dioxan), m. p. and mixed m. p. 109—110° (Found: C, 60·5; H, 10·7%). The residue from the steam-distillation was separated into intractable neutral (364 mg.) and acidic (100 mg.) fractions.

Rubropunctatamine (XVIII).—A solution of rubropunctatin (1 g.) in ether (350 ml.) was shaken for 1 min. with aqueous ammonia (*d* 0·88) (6 ml.) in water (250 ml.), the colour of the ether solution changing from orange to purple. After addition of concentrated hydrochloric acid (8 ml.), the ether layer was separated, the aqueous layer was further extracted with ether, and the combined ether extracts were concentrated (to *ca.* 240 ml.) and cooled. The dark purple crystals which separated were collected and recrystallised from a small volume of alcohol, giving *rubropunctatamine* in purple needles (660 mg.), m. p. 217—218° (decomp.), $\lambda_{max.}$ 252, 305, 382 (sh), 426, and 542 mμ (log ε 4·16, 4·43, 3·93, 4·17, and 4·24), $\nu_{max.}$ 3067m, 1715s, and 1706s (doublet), 1657w, 1626s, and 1550(s + b) cm.$^{-1}$ (Found: C, 71·3; H, 6·5; N, 4·0. $C_{21}H_{23}O_4N$ requires C, 71·4; H, 6·6; N, 4·0%). Rubropunctatamine was soluble in concentrated hydrochloric acid to a yellow solution, and was precipitated unchanged by water. The pigment, when suspended in alcohol, dissolved immediately on addition of 2N-sodium hydroxide, and was precipitated unchanged on acidification.

Dihydrorubropunctatamine.—(*a*) Hydrogenation of rubropunctatamine (1·0 g.) in alcohol (150 ml.) at atmospheric pressure with palladium–charcoal (from 50 mg. of palladium chloride and 500 mg. of charcoal) was allowed to proceed until 1·2 mols. of gas had been absorbed. On isolation, *dihydrorubropunctatamine* separated from alcohol in red needles (700 mg.), m. p. 212—213° (decomp.), $\lambda_{max.}$ 229, 243, 270, 418, and 503 mμ (log ε 4·15, 4·16, 4·19, 4·22, and 4·29), $\nu_{max.}$ 3070(m + b), 1715 and 1701s (doublet), and 1637s cm.$^{-1}$ (Found: C, 71·2; H, 7·3; N, 3·7. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·1; N, 3·9%).

(*b*) Dihydrorubropunctatin (504 mg.) was dissolved in aqueous ammonia (*d* 0·88; 15 ml.), and after ½ hr. at room temperature the solution was diluted with water (200 ml.) and acidified with hydrochloric acid. The resultant red precipitate was collected and crystallised from benzene–light petroleum (b. p. 80—100°), giving dihydropunctatamine in red needles (414 mg.), m. p. and mixed m. p. 212—213° (decomp.) (Found: C, 70·6; H, 7·2; N, 4·1%).

A suspension of this compound in alcohol dissolved immediately on addition of a drop of 2N-sodium hydroxide.

N-*Methylrubropunctatamine.*—Treatment of rubropunctatin (2 g.) in ether (750 ml.) with 25% aqueous methylamine (25 ml.) in water (500 ml.), as described for the preparation of rubropunctatamine, gave N-*methylrubropunctatamine* which separated from alcohol in almost black needles (1·05 g.), m. p. 209—210° (decomp.), $\nu_{max.}$ 1715s, and 1631s cm.$^{-1}$ (Found: C, 72·2; H, 7·0; N, 3·9. $C_{22}H_{25}O_4N$ requires C, 71·9; H, 6·9; N, 3·8%). A suspension of this compound in alcohol did not dissolve on addition of 2N-sodium hydroxide.

Ozonolysis of Rubropunctatamine.—A stream of ozone and oxygen was led into a solution of rubropunctatamine (500 mg.) in ethyl acetate (250 ml.) at room temperature until the original purple colour was discharged (1·5 hr.). During evaporation of the solvent *in vacuo* at room temperature the purple colour was restored. The residue was treated with water (25 ml.), and 12 hr. later the aqueous layer was decanted from the amorphous purple residue. Acetaldehyde

was isolated from the aqueous phase by distillation in steam, and characterised as the 2,4-dinitrophenylhydrazone, yellow needles (from alcohol), m. p. and mixed m. p. 164·5—166°.

Ozonolysis of dihydrorubropunctatamine under similar conditions gave a similar amorphous purple residue but no acetaldehyde.

Oxidation of Rubropunctatamine.—(a) *With nitric acid.* Rubropunctatamine (1 g.) was warmed at 100° with nitric acid (*d* 1·52; 6 ml.) and water (1 ml.) for 18 hr. with additions of more nitric acid (4·5 ml. and 7 ml.) after 5 hr. and 8 hr. The residue was evaporated with water (15 ml.) and subsequently dissolved in water (15 ml.), washed with ether, and boiled with a small amount of charcoal. After filtration, concentration to 4 ml. gave pale yellow prisms which recrystallised from hot water giving pyridine-2,4,5-tricarboxylic acid in prisms (340 mg.), m. p. and mixed m. p. 242—243° (decomp.) (after drying), having an infrared spectrum identical with that of an authentic sample.

(b) *With potassium permanganate.* Rubropunctatamine (1 g.), suspended in 3% aqueous sodium hydroxide (30 ml.) at room temperature, was treated with portions (5 ml.) of 5% aqueous potassium permanganate, reduction of each portion being complete before addition of the next. After addition of 70 ml. the mixture was warmed to 90° and further quantities of the reagent added until oxidation was complete (210 ml. in total). Hexanoic acid was separated by distillation in steam, isolated in ether, and characterised as the *p*-bromophenacyl ester (245 mg.), m. p. and mixed m. p. 69·5—71°.

Aporubropunctatamine (XII).—Successive portions of zinc dust (*ca.* 5 × 750 mg.) were added to rubropunctatamine (1·0 g.) in alcohol (100 ml.) and acetic acid (10 ml.) at 30—40° until the colour of the solution changed from purple to yellow-orange (*ca.* 5 min.). After filtration, the solution was poured into 2N-sodium hydrogen carbonate (300 ml.), and the resultant amorphous orange precipitate was collected and crystallised from alcohol (75 ml.) to give colourless needles (640 mg.) of *aporubropunctatamine*, m. p. 197—198° (red melt), unchanged on sublimation at 190°/0·5 mm., $[\alpha]_D$ ±0° (*c* 6·9 in pyridine), $\lambda_{max.}$ 261, 306, and 356 mμ (log ε 4·56, 3·85, and 3·69), $\nu_{max.}$ 3120m (phenolic OH), 1709s (isolated C=O), 1656w, 1626m, 1586m, and 1567s cm.$^{-1}$ (Found: C, 77·1; H, 8·0; N, 4·9; *C*-Me, 13·3. $C_{20}H_{25}O_2N$ requires C, 77·1; H, 8·1; N, 4·5; 3*C*-Me, 14·5%). In a second experiment under conditions designed to exclude carbon dioxide, carbon dioxide produced in the reduction was estimated by conversion into barium carbonate (Found: 561 mg. of $BaCO_3$ from 1·000 g. of rubropunctatamine. $1CO_2$ requires 558 mg. of $BaCO_3$). Aporubropunctatamine had the following properties: (*a*) A suspension in alcohol dissolved immediately on addition of 2N-sodium hydroxide, (*b*) addition of dilute hydrochloric acid gave a yellow solution of the hydrochloride, (*c*) a solution in methanol did not give iodoform, and (*d*) Gibb's reagent in pyridine gave an instantaneous bright blue colour. Prepared with acetic anhydride and pyridine, O-*acetylaporubropunctatamine* formed needles [from light petroleum (b. p. 60—80°)], m. p. 114—115°, $\lambda_{max.}$ 252, 290, 299, and 342 mμ (log ε 4·71, 4·16, 4·10, and 3·46) with shoulders at 280 and 353 mμ (log ε 4·07 and 3·39), $\nu_{max.}$ 1757s (phenolic OAc), 1704s (isolated ketonic C=O), 1639w, 1597w, 1572w, and 1205s (phenolic OAc) cm.$^{-1}$ (Found: C, 74·9; H, 7·6; N, 4·0. $C_{22}H_{27}O_3N$ requires C, 74·8; H, 7·7; N, 4·0%). This compound, in alcoholic suspension, did not dissolve in 2N-sodium hydroxide, but was soluble in dilute hydrochloric acid.

O-*Methylaporubropunctatamine.*—Aporubropunctatamine (500 mg.) in acetone (35 ml.) was heated under reflux for 2 hr. with methyl iodide (0·5 ml.) and potassium carbonate (800 mg.), more methyl iodide (0·25 ml.) being added after 1 hr. After cooling of the mixture, the potassium carbonate was collected and washed with hot acetone (3 × 10 ml.), and the combined filtrates were concentrated (to 5 ml.), diluted with water (15 ml.), and heated to boiling; the clear solution was then allowed to cool. The solid which separated was collected, dried, and extracted with hot light petroleum (b. p. 40—60°). On cooling, the extract deposited O-*methylaporubropunctatamine* (230 mg.) which on recrystallisation from light petroleum (b. p. 40—60°) gave needles, m. p. 80—81°, $\lambda_{max.}$ 253, 280, 290, 300, and 341 mμ (log ε 4·77, 4·09 4·09, 4·18, and 3·55), $\nu_{max.}$ 1704s (ketonic C=O), 1660w, 1631w, 1595w, and 1572m cm.$^{-1}$ (Found: C, 77·4; H, 8·4; N, 4·3; OMe, 8·8. $C_{21}H_{27}O_2N$ requires C, 77·5; H, 8·4; N, 4·3; OMe, 9·5%). Prepared with hydroxylamine hydrochloride and pyridine the *oxime* formed needles (from ether), m. p. 122—124° (Found: N, 7·9. $C_{21}H_{28}O_2N_2$ requires N, 8·2%).

N-*Methylaporubropunctatamine.*—(*a*) Aporubropunctatamine (1 g.) and methyl iodide (1 ml.) in acetone (75 ml.) were heated under reflux for 4 hr., and the resultant solution concentrated to 20 ml. *Aporubropunctatamine methiodide* (1·2 g.) separated as yellow prisms,

XUM

m. p. 218—219°, not raised by subsequent recrystallisation from ethanol and ether, $\lambda_{max.}$ 264, 330, and 401 mμ (log ε 4·19, 3·27, and 3·44), $\nu_{max.}$ 3195m (phenolic OH), 1706s (isolated ketonic C=O), 1626s, 1563m, and 1508w cm.$^{-1}$ (Found: C, 55·4; H, 6·5; N, 2·8; I, 28·1. $C_{21}H_{28}O_2NI$ requires C, 55·6; H, 6·2; N, 3·1; I, 28·0%). This compound (500 mg.) in methanol (10 ml.) with 2N-sodium carbonate (10 ml.) and water (30 ml.) gave a red precipitate of N-*methylaporubropunctatamine* which separated from ethyl acetate and light petroleum (b. p. 60—80°) in orange needles (330 mg.), m. p. 172—174°, $\lambda_{max.}$ 241, 370, and 481 mμ (log ε 4·51, 3·78, and 3·85) with an inflexion at 275 mμ (log ε 4·32), $\nu_{max.}$ 1701s (isolated ketonic C=O), 1623s, and 1563m cm.$^{-1}$ (Found: C, 76·9; H, 8·4; N, 4·3. $C_{21}H_{27}O_2N$ requires C, 77·5; H, 8·4; N, 4·3%).

(*b*) Reduction of *N*-methylrubropunctatamine (1 g.) with zinc and acetic acid, according to the method for the preparation of aporubropunctatamine, gave *N*-methylaporubropunctatamine in orange needles (500 mg.) [from benzene and light petroleum (b. p. 60—80°)], m. p. and mixed m. p. 173·5—174° (Found: C, 77·4; H, 8·4; N, 4·7%).

Dihydroaporubropunctatamine.—(*a*) Hydrogenation of aporubropunctatamine (1·0 g.) in alcohol (150 ml.) with 10% palladium–charcoal (500 mg.) at atmospheric pressure was terminated when *ca.* 1·2 mols. had been absorbed. *Dihydroaporubropunctatamine* formed needles (660 mg.) (from alcohol), m. p. 118—119°, $\lambda_{max.}$ 238, and 343 mμ (log ε 4·69, and 3·69), $\nu_{max.}$ 3145m (phenolic OH), 1708s (ketonic C=O), 1639m, 1599w, and 1560s cm.$^{-1}$ (Found: C, 76·8; H, 8·8; N, 4·5. $C_{20}H_{27}O_2N$ requires C, 76·6; H, 8·7; N, 4·5%).

(*b*) Reduction of dihydrorubropunctatamine (0·5 g.) with zinc and acetic acid by the usual method gave dihydroaporubropunctatamine (0·3 g.), m. p. and mixed m. p. 118—119°, having an infrared spectrum identical with the compound prepared as in (*a*). Prepared with acetic anhydride and pyridine O-*acetyldihydroaporubropunctatamine* formed needles [from light petroleum (b. p. 60—80°)], m. p. 82—83°, $\lambda_{max.}$ 232, 268, 321, and 334 mμ (log ε 4·79, 3·60, 3·48, and 3·54), $\nu_{max.}$ 1754s (phenolic OAc), 1708s (isolated ketonic C=O), 1642w, 1600w, 1568w, and 1225s (phenolic OAc) cm.$^{-1}$ (Found: C, 74·0; H, 8·1; N, 4·1. $C_{22}H_{29}O_3N$ requires C, 74·3; H, 8·2; N, 3·9%).

Reduction of Aporubropunctatamine, its Dihydro-derivative, and O-Methyl Derivative with Potassium Borohydride.—To a suspension of aporubropunctatamine (250 mg.) in methanol (10 ml.) and water (2 ml.) was added 2N-sodium hydroxide until a homogeneous solution was obtained. Potassium borohydride (250 mg.) in water (5 ml.) was then added, and the mixture kept at 35—40° for 6 hr., then kept at room temperature for 18 hr. Acidification with acetic acid and crystallisation of the precipitate from methanol gave prisms (180 mg.) of the *dialcohol*, m. p. 207—208°, $\lambda_{max.}$ 259, 308, and 352 mμ (log ε 4·68, 3·82, and 3·63), $\nu_{max.}$ 3300m (alcoholic OH), 3106m (phenolic OH), 1626s, 1585m, and 1560s cm.$^{-1}$ (Found: C, 76·1; H, 8·8; N, 4·4. $C_{20}H_{27}O_3N$ requires C, 76·6; H, 8·7; N, 4·5%). With acetic anhydride and pyridine, the reduction product formed a *di*-O-*acetate*, needles (from aqueous alcohol), m. p. 91—92°, $\lambda_{max.}$ 252, 290, 300, 343, and 354 mμ (log ε 4·72, 4·11, 4·08, 3·47, and 3·42), $\nu_{max.}$ (in CCl_4) 1773s and 1190s (phenolic OAc), 1733s and 1220s (alcoholic OAc), and 1626m cm.$^{-1}$ (Found: C, 72·3; H, 7·8; N, 3·8. $C_{24}H_{31}O_4N$ requires C, 72·5; H, 7·9; N, 3·5%).

Similar treatment of dihydroaporubropunctatamine (1·3 g.) with potassium borohydride gave the *dihydro-derivative* of the above reduction product, rhombs (910 mg.) (from aqueous alcohol), m. p. 164—165°, $\lambda_{max.}$ 241 and 343 mμ (log ε 4·69, and 3·66), $\nu_{max.}$ 3289m (alcoholic OH), 3125m (phenolic OH), 1628s, 1592m, and 1562s cm.$^{-1}$ (Found: C, 75·9; H, 9·4; N, 4·6. $C_{20}H_{29}O_3N$ requires C, 76·1; H, 9·3; N, 4·4%). The *di*-O-*acetate* formed needles (from aqueous alcohol), m. p. 97—99°, $\lambda_{max.}$ 231, 269, 321, and 333 mμ (log ε 4·93, 3·62, 3·54, and 3·60), $\nu_{max.}$ (in CCl_4) 1773s and 1190s (phenolic OAc), 1730s and 1220m (alcoholic OAc), and 1623m cm.$^{-1}$ (Found: C, 72·6; H, 8·5; N, 3·6; Ac, 22·0. $C_{24}H_{33}O_4N$ requires C, 72·2; H, 8·3; N, 3·5; Ac, 21·5%).

Prepared by methylation of the above reduction product from aporubropunctatamine with methyl iodide and potassium carbonate in acetone, or by reduction of *O*-methylaporubropunctatamine with sodium borohydride, the *methoxy-alcohol* separated from aqueous methanol in needles, m. p. 94—95°, $\lambda_{max.}$ 254, 292, 304, and 342 mμ (log ε 4·73, 4·00, 3·93, and 3·52) with an inflection at 354 mμ (log ε 3·47), $\nu_{max.}$ 3289m (alcoholic OH), 1650w, 1623s, 1580m, and 1653s cm.$^{-1}$ (Found: C, 76·7; H, 8·7; N, 4·3; OMe, 9·2. $C_{21}H_{29}O_2N$ requires C, 77·0; H, 8·9; N, 4·3; OMe, 9·5%). The O-*acetate* formed needles (from aqueous methanol), m. p. 79—80°, $\lambda_{max.}$ 253, 292, 303, 343, and 353 mμ (log ε 4·74, 4·07, 4·01, 3·52, and 3·47), $\nu_{max.}$ (in CCl_4) 1733s and 1233s (alcoholic OAc), 1647w, 1618m, 1575m, and 1558 cm.$^{-1}$ (Found: C, 74·7; H, 8·8; N, 3·8. $C_{23}H_{31}O_3N$ requires C, 74·8; H, 8·5; N, 3·8%).

XUM

Ozonolysis of O-Acetylaporubropunctatamine.—This compound (1·0 g.) in ethyl acetate (100 ml.) at room temperature was treated with ozone and oxygen until the yellow colour initially formed in the solution had faded (*ca.* 20 min.). After evaporation of the solvent *in vacuo*, the residue was treated with water (20 ml.), and 12 hr. later the brown precipitate was collected and crystallised from methanol, giving the *bisnor-acid* in needles (220 mg.), m. p. 244°, $\nu_{max.}$ 2500(w + b) (CO_2H), 1750s and 1196s (phenolic OAc), and 1700s (CO_2H and isolated ketonic C=O) cm.$^{-1}$ (Found, after thorough drying: C, 67·0; H, 6·7; N, 3·9; O, 22·3. $C_{30}H_{23}O_5N$ requires C, 67·2; H, 6·5; N, 3·9; O, 22·4%). Prepared with diazomethane the *methyl ester* formed needles, m. p. 145—146° (from methanol), $\nu_{max.}$ 3370w (solvate water), 1767s (phenolic OAc), 1715s (Me ester and ketonic C=O), 1629w, and 1567w cm.$^{-1}$ (Found: C, 66·1; H, 6·7; N, 3·7. $C_{31}H_{25}O_5N,0·5H_2O$ requires C, 66·3; H, 6·9; N, 3·7%). The aqueous filtrate left after separation of the bisnor-acid was distilled in steam; acetaldehyde was isolated from the distillate as the 2,4-dinitrophenylhydrazone, yellow needles (0·17 g. 33%) (from alcohol), m. p. and mixed m. p. 166—166·5°.

Azo-dye from the Borohydride Reduction Product of Aporubropunctatamine.—A solution (40 ml.) of benzenediazonium chloride was prepared in the usual way at 0° from aniline (1·28 g.). Part (2 ml.) of this solution was added dropwise at 0° to a stirred solution of the borohydride reduction product from aporubropunctatamine (218 mg.) in N-sodium hydroxide (10 ml.) and methanol (10 ml.). The resultant deep red solution was neutralised with 20% acetic acid, and the red precipitate collected and crystallised from alcohol, giving orange needles (150 mg.) of the *azo-dye*, m. p. 194° (decomp.), $\lambda_{max.}$ 251, 409, and 486 mμ (log ε 4·44, 4·03, and 4·16), $\nu_{max.}$ 3310m (alcoholic OH), 3086sh (phenolic OH), 1645w, 1608m, and 1548s cm.$^{-1}$ (Found, after thorough drying: C, 74·6; H, 7·7; N, 10·1. $C_{26}H_{31}O_2N_3$ requires C, 74·8; H, 7·5; N, 10·1%). This compound, when suspended in a small amount of methanol or ether, dissolved immediately on addition of dilute sodium hydroxide to give an intense red colour. The original orange colour was restored by acidification.

The Cinnoline Derivative (XV).—Part (2 ml.) of a benzenediazonium chloride solution [from aniline (1·28 g.) in a total volume of 40 ml.] was added dropwise at 0° to aporubropunctatamine (216·5 mg.) in N-sodium hydroxide (10 ml.) and methanol (15 ml.). Coagulation of the red precipitate, which separated immediately, was effected by neutralisation with 20% acetic acid, and the product was collected and crystallised from alcohol, giving the *cinnoline derivative* (XV) in vermillion red needles (223 mg.) m. p. 233—234°, $\lambda_{max.}$ 249, 280, 325, 408, and 443 mμ (log ε 4·49, 4·32, 4·03, 4·29, and 4·10), $\nu_{max.}$ 1645w, 1618w, 1592s, 1582s, 1567s, and 1536m cm.$^{-1}$ (Found, after thorough drying: C, 78·6; H, 7·0; N, 10·8. $C_{26}H_{27}ON_3$ requires C, 78·6; H, 6·9; N, 10·6%). This compound, when suspended in a small amount of methanol or ether, did not dissolve or change colour on addition of dilute sodium hydroxide.

Hexahydroaporubropunctatin (XXIa).—Hydrogenation of rubropunctatin (500 mg.) in acetic acid (100 ml.) at atmospheric pressure with 10% palladium–carbon (500 mg.) was complete after the apparent absorption of 5—6 mols. A solution of the product (a pale yellow oil) in ether was successively extracted with saturated sodium hydrogen carbonate and 2N-sodium hydroxide solutions, and the products were recovered by acidification of the extracts and separation in ether. The " acidic " (trace) and " phenolic " (70 mg.) extracts were intractable and were discarded. The " neutral " material (360 mg.) was adsorbed on a column of silica gel (4" × ½") from solution in benzene–light petroleum (b. p. 60—80°) (1 : 1) (10 ml.). Successive elution with the same solvent mixture (2 × 40 ml.) and benzene (2 × 40 ml.) gave *hexahydroaporubropunctatin* (XXIa) which separated from light petroleum in needles (60 mg.), m. p. 76—77°, $\lambda_{max.}$ 282 mμ (log ε 3·36), $\nu_{max.}$ 3663m (phenolic OH), 1718s (isolated ketonic C=O), and 1626w cm.$^{-1}$ (Found: C, 75·7, 75·6; H, 9·3, 9·5; *C*-Me, 12·3. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5; 3*C*-Me, 14·2%). Further elution with more polar solvents gave only intractable material. With acetic anhydride and pyridine the phenol (XXIa) gave an *acetate* (XXIb) which separated from aqueous alcohol in needles, m. p. 71·5—72·5°, $\lambda_{max.}$ 266 mμ (log ε 2·55), $\nu_{max.}$ (in CCl_4) 1761s and 1193s (phenolic OAc), 1706s (isolated ketonic C=O), and 1616w cm.$^{-1}$ (Found: C, 73·3; H, 9·0. $C_{22}H_{32}O_4$ requires C, 73·3; H, 9·0%). With dimethyl sulphate and potassium carbonate in acetone the phenol (XXIa) gave a *methyl ether* (XXIc), needles (from aqueous alcohol), m. p. 49—50°, $\lambda_{max.}$ 272 mμ (log ε 2·62) (Found: C, 75·9; H, 9·8; OMe, 9·1. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7; OMe, 9·3%). With hydroxylamine hydrochloride and pyridine the methyl ether gave an *oxime*, needles (from aqueous alcohol), m. p. 80—81° (Found: C, 72·6; H, 9·7; N, 4·2. $C_{21}H_{33}O_3N$ requires C, 72·6; H, 9·6; N, 4·1%).

XUM

Reduction of Hexahydroaporubropunctatin with Potassium Borohydride.—Hexahydroaporubropunctatin (100 mg.) in methanol (10 ml.) was treated with potassium borohydride (50 mg.) in water (5 ml.) for 16 hr. at room temperature. After acidification with 2N-hydrochloric acid (10 ml.) and water (50 ml.) the precipitate was collected and crystallised from aqueous alcohol, giving the *dialcohol* (XXIIa) in plates (70 mg.), m. p. 99—100°, $\lambda_{max.}$ 274, and 282 mμ (log ε 2·98, and 3·00), $\nu_{max.}$ 3379m and 1587w cm.$^{-1}$ (Found: C, 74·7; H, 10·5. $C_{20}H_{32}O_8$ requires C, 75·0; H, 10·1%). Prepared with acetic anhydride and pyridine, the *diacetate* (XXIIb) separated from aqueous alcohol in needles, m. p. 62—63°, $\lambda_{max.}$ 268mμ (log ε 2·56), $\nu_{max.}$ 1773s and 1196s (phenolic OAc), 1736s and 1238s (alcoholic OAc), 1626w, and 1575w cm.$^{-1}$ (Found: C, 71·8; H, 9·4. $C_{24}H_{36}O_8$ requires C, 71·3; H, 9·0%).

Oxidation of Hexahydro-O-methylaporubropunctatin.—A solution of this compound (250 mg.) in acetone (25 ml.) was heated under reflux during the addition of potassium permanganate (1·2 g.), in small portions, during 14 hr. After distillation of acetone from the mixture, the residue was treated with water (25 ml.) and sulphur dioxide. The product was isolated in ether and extracted with saturated sodium hydrogen carbonate solution. Acidification of this extract with 2N-hydrochloric acid gave a white precipitate which was collected and crystallised from water, giving the *acid* (XXIII) in needles (25 mg.), m. p. 151—152°, $\nu_{max.}$ 2646m and 1698s (aryl CO_2H), 1718s (δ-lactone of aryl acid), 1600w, and 1563w cm.$^{-1}$ (Found: C, 64·4; H, 6·7; OMe, 11·1. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5; OMe, 11·1%).

The authors are indebted to Drs. F. M. Dean, W. B. Whalley, and Mr. J. Staunton of this Department for helpful discussions and for information about unpublished work on rotiorin. One of them (E. J. H.) thanks the Department of Scientific and Industrial Research for a Maintenance Grant. The microanalyses were performed by Mr. A. S. Inglis, M.Sc., and his associates of this Department.

UNIVERSITY OF LIVERPOOL. [*Received, June 4th,* 1959.]

---

723. *Bis-o-phenylene Pyrophosphite: A New Reagent for Peptide Synthesis. Part II.* Some Peptide Syntheses with the New Reagent.*

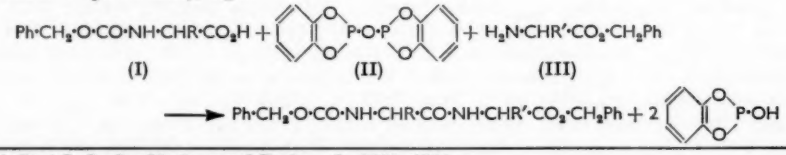
By P. C. CROFTS, J. H. H. MARKES, and H. N. RYDON.

The use of bis-*o*-phenylene pyrophosphite as a reagent for the synthesis of peptides is described. The experimental procedure is simple and the yields are good, and, although racemisation occurs in certain circumstances, the new method is recommended for general use.

Ester-interchange during the catalytic hydrogenolysis of peptide benzyl esters can be avoided by using t-butyl alcohol as solvent.

IN Part I * we described the preparation of bis-*o*-phenylene pyrophosphite (II), in good yield and by a simple procedure, from catechol and phosphorus trichloride. We now describe the use of this reagent in peptide syntheses, as a substitute for the widely used, but less easily prepared, tetraethyl pyrophosphite.[1,2]

As with tetraethyl pyrophosphite,[1] so with the new reagent, peptide syntheses can be carried out either by direct interaction of the reagent with the two reactants (the "standard" procedure), *e.g.*:



* Part I, Crofts, Markes, and Rydon, *J.*, 1958, 4250.

[1] Anderson, Blodinger, and Welcher, *J. Amer. Chem. Soc.*, 1952, **74**, 5309.

[2] For some important synthetical applications of tetraethyl pyrophosphite see, *inter alia*, Anderson, *ibid.*, 1953, **75**, 6081; du Vigneaud, Ressler, Swan, Roberts, and Katsoyannis, *ibid.*, 1954, **76**, 3115; Gish and du Vigneaud, *ibid.*, 1957, **79**, 3579; Ressler and du Vigneaud, *ibid.*, p. 4511; Katsoyannis, Gish, and du Vigneaud, *ibid.*, p. 4516.

or by so-called " anhydride " or " amide " procedure, involving preliminary reaction of the pyrophosphite with, respectively, the carboxyl (I), or amino-component (III), followed by reaction of the resulting mixed anhydride or phosphoramidite with the second reactant, (III) or (I).

The " standard " procedure is by far the most convenient of the three, and we have not found either of the alternatives to possess any marked advantages in the cases we have investigated. Tetraethyl pyrophosphite is generally used in diethyl hydrogen phosphite as solvent; with bis-*o*-phenylene pyrophosphite, the more readily available pyridine has been satisfactory † and has the advantage that amino-acid or peptide esters can be used as their hydrohalides or toluene-*p*-sulphonates. The experimental procedure is very simple, an *N*-protected (*N*-benzyloxycarbonyl- or *N*-phthaloyl-) amino-acid or peptide, *e.g.*, (I), and an equimolecular amount of an amino-acid or peptide ester, *e.g.*, (III), conveniently, although not necessarily, as its hydrochloride or toluene-*p*-sulphonate, being heated in pyridine on the steam-bath for half an hour with a 10% excess of bis-*o*-phenylene pyrophosphite; the cooled mixture is then poured into water, and the product isolated by an appropriate procedure.

In the following Table are recorded the yields, of purified product, obtained in seventeen peptide syntheses carried out by this " standard " procedure (the arrangement and abbreviations are those used by Goodman and Kenner,[4] *e.g.*, Z = Ph·CH_2·O·CO–). It will be seen that the yields are, in general, very satisfactory; excluding the tyrosine peptides and the experiments in which extensive racemisation occurred, the average yield of purified material is 67%; in most cases the crude product, obtained in substantially higher yield, is sufficiently pure for preparative purposes. The method is unsuitable for the synthesis of tyrosine peptides without prior protection of the phenolic hydroxyl group; this is not wholly unexpected in view of the ease with which this hydroxyl group undergoes *O*-phosphorylation.[5]

Product	Reactants	Yield (%)
Z·Gly·Leu·OMe	Z·Gly·OH; H·Leu·OMe	88
Z·Gly·Leu·OBz	Z·Gly·OH; H·Leu·OBz	76
Phth·Gly·Tyr·OBz	Phth·Gly·OH; H·Tyr·OBz	21
Z·Gly·Gly·Cys(SBz)·OBz	Z·Gly·Gly·OH; H·Cys(SBz)·OBz	74
Z·Cys(SBz)·Gly·Gly·OEt	Z·Cys(SBz)·OH; H·Gly·Gly·OEt	52
Z·Cys(SBz)·Gly·Gly·OBz	Z·Cys·(SBz)·OH; H·Gly·Gly·OBz	56
Z·Gly·Gly·Gly·OBz	Z·Gly·Gly·OH; H·Gly·OBz	79
Z·Leu·Gly·Gly·OBz	Z·Leu·OH; H·Gly·Gly·OBz	69
Z·Met·Gly·Gly·OBz	Z·Met·OH; H·Gly·Gly·OBz	59
Z·Tyr·Gly·Gly·OBz	Z·Tyr·OH; H·Gly·Gly·OBz	25
Z·Gly·Leu·Gly·OBz	Z·Gly·Leu·OH; H·Gly·OBz	38 *
Phth·Gly·Tyr·Gly·OBz	Phth·Gly·Tyr·OH; H·Gly·OBz	14 *
Z·Gly·Gly·Leu·OBz	Z·Gly·Gly·OH; H·Leu·OBz	70
Z·Gly·Gly·Met·OBz	Z·Gly·Gly·OH; H·Met·OBz	40
Z·Gly·Gly·Phe·OBz	Z·Gly·Gly·OH; H·Phe·OBz	70
Z·Gly·Gly·Tyr·OBz	Z·Gly·Gly·OH; H·Tyr·OBz	45
Z·Gly·Gly·Gly·Gly·OBz	Z·Gly·Gly·OH; H·Gly·Gly·OBz	70

* Product extensively racemised.

It is of considerable importance to know in what circumstances a peptide synthesis may be accompanied by racemisation and we have accordingly examined this aspect. As with other methods, no racemisation occurred when the amino-component, *e.g.*, (III), alone contained an asymmetric centre or in coupling *N*-benzyloxycarbonyl-L-amino-acids

† Since our work was completed, Maclaren [3] has reported the use of pyridine as a solvent in syntheses with tetraethyl pyrophosphite.

[3] Maclaren, *Australian J. Chem.*, 1958, **11**, 360.
[4] Goodman and Kenner, *Adv. Protein Chem.*, 1957, **12**, 465; cf. Erlanger and Brand, *J. Amer. Chem. Soc.*, 1951, **73**, 3508.
[5] Ashbolt and Rydon, *Biochem. J.*, 1957, **66**, 237.

XUM

with amino-acid or peptide esters; this point was established in the coupling of *N*-benzyloxycarbonylglycylglycine with L-leucine benzyl ester, and of *N*-benzyloxycarbonyl-L-leucine with glycylglycine benzyl ester, by the rigorous method of hydrogenolysis of the product, followed by complete hydrolysis and examination of the optical rotatory power of the hydrolysate, rather than the usual, but less conclusive, method of comparing the optical rotatory power of the product with that of a specimen made by a method known, or presumed, not to cause racemisation. As in syntheses by other reagents,[6] however, extensive racemisation occurred in coupling carboxyl components of the type X·NH·CHR·CO·NH·CHR′·CO_2H, possibly owing to oxazolone formation;[6,7] racemisation occurs similarly with tetraethyl pyrophosphite.[1] With our reagent, racemisation was observed when the " amide " and the " anhydride " procedure were used, as well as in the " standard " conditions; racemisation was not suppressed when pyridine was replaced by diethyl phosphite as solvent.

During this work, we synthesised diglycyl-L-leucine by way of L-leucine benzyl ester toluene-*p*-sulphonate and *N*-benzyloxycarbonyldiglycyl-L-leucine benzyl ester; by a coincidence, both intermediates exhibited zero rotation, although the final product was shown, by the hydrolysis procedure already mentioned, to have full optical activity.

The new method of peptide synthesis described in this paper has a number of advantages; the experimental procedure is very simple and the reagent used is easily prepared and may be purified by vacuum-distillation and stored indefinitely in a stoppered bottle. Since the method was first developed, in 1955, it has been used extensively by colleagues for many peptide syntheses, in addition to those described in the present paper; at present it is one of the three methods which we generally prefer for peptide synthesis, the others being the azide [8] and the carbodi-imide [9] method.

Benzyl esters are frequently used, particularly in conjunction with *N*-benzyloxycarbonyl groups, in peptide synthesis, both protecting groups being eventually removed by catalytic hydrogenolysis, generally in ethanol or aqueous ethanol, often with the addition of acetic acid. In this work, we observed that catalytic hydrogenolysis of *N*-benzyloxycarbonyldiglycyl-leucine benzyl ester and of *N*-benzyloxycarbonyl-leucylglycylglycine benzyl ester was not entirely satisfactory in ethanolic solvents, the products being contaminated with some tripeptide ethyl ester; similar difficulties have been encountered in other cases. This unwanted ester-interchange can be entirely avoided by using t-butyl alcohol in place of ethanol and we recommend this as a general procedure.

Experimental

Pyridine was dried for some weeks over potassium hydroxide, shaken overnight with freshly ignited barium oxide, and then distilled over barium oxide. Light petroleum denotes the fraction of b. p. 60—80°. Rotations were measured in 2 dm. tubes. The purity of all products was checked by chromatography on Whatman No. 1 paper, with butan-1-ol–pyridine–water (39 : 21 : 39) or butan-1-ol–acetic acid–water (100 : 17 : 38) as developing solvent.

*Benzyl Ester Toluene-*p*-sulphonates.*—The following modified procedure [10,11] was used: The amino-acid or peptide (0·1 mole) and toluene-*p*-sulphonic acid monohydrate (0·1 mole) were refluxed with benzyl alcohol (100—250 ml.) in 1—4 volumes of benzene in an apparatus fitted with a Dean and Stark tube to remove entrained water. Refluxing was continued for some hours after water ceased to be produced; benzene and some excess of benzyl alcohol were removed under reduced pressure (max. temperature 125°), and the residue was ground and slurried with ether. The insoluble product was then recrystallised.

[6] Kenner, *Chem. Soc. Special Publ.*, 1955, **2**, 103; cf. Goodman and Kenner, ref. 4.
[7] Young, Wood, Joyce, and Anderson, *J. Amer. Chem. Soc.*, 1956, **78**, 2126.
[8] Curtius, *Ber.*, 1902, **35**, 3226.
[9] Sheehan and Hess, *J. Amer. Chem. Soc.*, 1955, **77**, 1067; Khorana, *Chem. and Ind.*, 1955, 1087; Sheehan, Goodman, and Hess, *J. Amer. Chem. Soc.*, 1956, **78**, 1367.
[10] Miller and Waelsch, *J. Amer. Chem. Soc.*, 1952, **74**, 1092; Cipera and Nicholls, *Chem. and Ind.*, 1955, 16.
[11] Hooper, Rydon, Schofield, and Heaton, *J.*, 1956, 3148.

The following were prepared in this way:

Glycine benzyl ester toluene-p-*sulphonate* (83%), m. p. 132°, from methanol–di-isopropyl ether (Found: C, 57·0; H, 5·5; N, 4·0. $C_{16}H_{19}O_5NS$ requires C, 57·0; H, 5·7; N, 4·2%).

Glycylglycine benzyl ester toluene-*p*-sulphonate (this compound was first prepared in these laboratories by Dr. D. Morris [12]), m. p. 153° (from ethanol) (76% yield).

L-*Leucine benzyl ester toluene*-p-*sulphonate* (74%), m. p. 157° (from benzene–light petroleum), $[\alpha]_D^{23\cdot5}$ 0·0° (*c* 2·00 in ethanol) (Found: C, 60·8; H, 7·1; N, 3·9. $C_{20}H_{27}O_5NS$ requires C, 61·0; H, 6·9; N, 3·6%); this salt was precipitated from the reaction mixture with light petroleum.

DL-*Methionine benzyl ester toluene*-p-*sulphonate* (60%), m. p. 129—131° (from ethyl acetate) (Found: C, 55·3; H, 6·2; N, 3·5. $C_{19}H_{25}O_5NS_2$ requires C, 55·4; H, 6·1; N, 3·4%).

DL-*Phenylalanine benzyl ester toluene*-p-*sulphonate* (59%), m. p. 149° (from water) (Found: C, 65·2; H, 5·7; N, 3·4. $C_{23}H_{25}O_5NS$ requires C, 64·6; H, 5·9; N, 3·3%).

L-Tyrosine benzyl ester toluene-*p*-sulphonate (this compound was first prepared in these laboratories by Dr. D. Morris [12]), m. p. 178° (from water), $[\alpha]_D^{23}$ −10·3° (*c* 1·00 in 60% acetone) (85% yield) (Found: C, 62·3; H, 5·4; N, 3·4. Calc. for $C_{23}H_{25}O_6NS$: C, 62·3; H, 5·7; N, 3·2%).

Peptide Syntheses.—Unless otherwise stated, the following, "standard," procedure was employed:

Equimolecular amounts of the carboxylic acid and amino-reactants, in anhydrous pyridine, were treated with bis-*o*-phenylene pyrophosphite (10% excess) (calcium chloride guard-tube). The mixture was then heated on a steam-bath for 30 min., cooled, and poured into ice and water. Next morning, the product was separated. If solid, it was filtered off, washed with N-sodium hydrogen carbonate, N-hydrochloric acid, and water, dried, and recrystallised; if an oil, it was dissolved in ethyl acetate, washed similarly, dried, and recovered.

In the "amide" procedure, the amino-reactant was heated, in pyridine, on the steam-bath for 2 min. with bis-*o*-phenylene pyrophosphite before addition of the carboxylic acid reactant. In the "anhydride" procedure, the carboxylic acid reactant and the pyrophosphite were similarly heated together for 2 min. before addition of the amine reactant.

N-*Benzyloxycarbonylglycyl*-L-*leucine Benzyl and Methyl Ester.*—*N*-Benzyloxycarbonylglycine [13] (8·37 g.) and L-leucine benzyl ester toluene-*p*-sulphonate (15·74 g.) were coupled in pyridine (25 ml.) by using bis-*o*-phenylene pyrophosphite (12·94 g.). The product (16·1 g., 98%) was an oil. Reprecipitation from ethyl acetate with light petroleum gave the *peptide benzyl ester* as an oil (12·6 g., 76%), $[\alpha]_D^{19}$ −11·1° (*c* 2·39 in ethyl acetate) (Found: C, 67·5; H, 7·1; N, 6·1. $C_{23}H_{28}O_5N_2$ requires C, 67·0; H, 6·8; N, 6·8%).

The *methyl ester*, prepared similarly in 88% yield from L-leucine methyl ester hydrochloride,[14] was an oil, $[\alpha]_D^{20\cdot5}$ −9·0° (*c* 2·05 in dioxan) (Found: C, 60·8; H, 7·0; N, 7·7. $C_{17}H_{24}O_5N_2$ requires C, 60·7; H, 7·2; N, 8·3%). Saponification (shaking for 45 min. with N-sodium hydroxide, followed by acidification) afforded *N*-benzyloxycarbonylglycyl-L-leucine (31%, after recrystallisation from aqueous ethanol), m. p. 102°, $[\alpha]_D^{20}$ −18·3° (*c* 1·39 in N-sodium hydroxide) (Vaughan [15] gives m. p. 99—100°, and Goldschmidt and Lautenschlager [16] give m. p. 104°, $[\alpha]_D^{14\cdot5}$ −17·9°).

N-*Phthaloyglycyl*-L-*tyrosine Benzyl Ester.*—N-Phthaloylglycine [17] (6·15 g.) and L-tyrosine benzyl ester toluene-*p*-sulphonate (13·30 g.) were coupled in pyridine (20 ml.), by using bis-*o*-phenylene pyrophosphite (9·70 g.). Several recrystallisations of the crude product (8·20 g., 60%), m. p. 172—176°, from ethyl acetate–light petroleum gave the pure *peptide benzyl ester* (2·88 g., 21%), m. p. 189°, $[\alpha]_D^{19}$ +54·4° (*c* 1·43 in ethyl acetate) (Found: N, 6·5. $C_{26}H_{22}O_6N_2$ requires N, 6·1%). Shaking this ester (4·50 g.), in ethanol (150 ml.) and water (30 ml.), in hydrogen, with 5% palladised charcoal, gave *N*-phthaloylglycyl-L-tyrosine (2·42 g., 67%), m. p. 257—258° (from methanol–di-isopropyl ether), $[\alpha]_D^{21}$ +75·0° (*c* 1·00 in 80% acetone (Turner [18] gives m. p. 241—244° and Hanson and Illhardt [19] give m. p. 235—237°).

N-*Benzyloxycarbonyldiglycyl*-S-*benzyl*-L-*cysteine Benzyl Ester.*—*N*-Benzyloxycarbonylglycylglycine [13] (2·66 g.) and *S*-benzyl-L-cysteine benzyl ester toluene-*p*-sulphonate [11] (4·73 g.) were

[12] Morris, Ph.D. Thesis, Manchester, 1956.
[13] Bergmann and Zervas, *Ber.*, 1932, **65**, 1192.
[14] Schott, Larkin, Rockland, and Dunn, *J. Org. Chem.*, 1947, **12**, 490.
[15] Vaughan, *J. Amer. Chem. Soc.*, 1952, **74**, 6137.
[16] Goldschmidt and Lautenschlager, *Annalen*, 1953, **580**, 68.
[17] Drechsel, *J. prakt. Chem.*, 1883, **27**, 418.
[18] Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 2388.
[19] Hanson and Illhardt, *Z. physiol. Chem.*, 1954, **298**, 210.

XUM

coupled in pyridine (10 ml.), by using bis-*o*-phenylene pyrophosphite (3·23 g.). Recrystallisation of the solid product (4·84 g., 88%), m. p. 109—111°, from ethyl acetate–light petroleum gave the pure peptide ester (4·05 g.; 74%), m. p. 115·5—116·5°, $[\alpha]_D^{22\cdot5}$ −35·0° (*c* 0·54 in ethanol) (Lautsch and Kraege [20] give m. p. 115·5—116·5°, $[\alpha]_D^{21}$ −32·3°).

*N-Benzyloxycarbonyl-S-benzyl-*L*-cysteinylglycylglycine Benzyl and Ethyl Esters.*—*N*-Benzyloxycarbonyl-*S*-benzyl-L-cysteine [21] (1·725 g.) and glycylglycine benzyl ester toluene-*p*-sulphonate (1·975 g.) were coupled in pyridine (3·5 ml.), by using bis-*o*-phenylene pyrophosphite (1·615 g.). The crude product (2·22 g., 78%), m. p. 120—123°, recrystallised from aqueous ethanol, affording the *peptide benzyl ester monohydrate* (1·58 g., 56%), m. p. 135°, $[\alpha]_D^{18}$ −14·7° (*c* 1·01 in ethyl acetate) (Found: C, 61·6, 62·1, 61·7; H, 5·7, 6·0, 5·8; N, 7·5; S, 5·5. $C_{29}H_{31}O_6N_3S,H_2O$ requires C, 61·4; H, 5·9; N, 7·4; S, 5·6%).

The ethyl ester, prepared similarly from glycylglycine ethyl ester hydrochloride, in 52% yield, and recrystallised from ethyl acetate–light petroleum, had m. p. 111—113°, $[\alpha]_D^{18}$ −12·0° (*c* 3·21 in ethanol) (Hooper *et al.*[11] give m. p. 114°, $[\alpha]_D^{20}$ −12·9°).

N-Benzyloxycarbonyldiglycylglycine Benzyl Ester.—*N*-Benzyloxycarbonylglycylglycine [13] (2·66 g.) and glycine benzyl ester toluene-*p*-sulphonate (3·37 g.) were coupled in pyridine (10 ml.) by using bis-*o*-phenylene pyrophosphite (3·23 g.). The crude product (3·84 g., 93%), m. p. 156—158°, recrystallised from aqueous ethanol, affording the peptide ester (3·28 g., 79%), m. p. 161° (Found: C, 61·2; H, 5·7; N, 10·2. Calc. for $C_{21}H_{23}O_6N_3$: C, 61·1; H, 5·6; N, 10·2%) (Hooper *et al.*[11] give m. p. 148° for material prepared by the mixed anhydride procedure).

*N-Benzyloxycarbonyl-*L*-leucylglycylglycine Benzyl Ester.*—*N*-Benzyloxycarbonyl-L-leucine [22] (7·95 g.) and glycylglycine benzyl ester toluene-*p*-sulphonate (11·82 g.) were coupled in pyridine (21 ml.) by using bis-*o*-phenylene pyrophosphite (9·70 g.). The crude product (10·4 g., 74%), m. p. 115—117°, $[\alpha]_D^{21}$ −11·0° (*c* 2·00 in dioxan), recrystallised from ethyl acetate–light petroleum, yielding the *peptide ester* (9·7 g., 69%), m. p. 117—118°, $[\alpha]_D^{21}$ −11·7° (*c* 2·00 in dioxan) (Found: C, 63·3, 63·4; H, 6·8, 6·9; N, 8·9. $C_{25}H_{31}O_6N_3$ requires C, 63·9; H, 6·7; N, 9·0%); two further recrystallisations, thorough washing with N-sodium hydrogen carbonate and a further recrystallisation removed a little yellow impurity, raising the m. p. to 122—123°, but leaving $[\alpha]_D$ unchanged. A similar yield was obtained by the " amide " procedure.

This ester (5·30 g.), in t-butyl alcohol (150 ml.) and water (30 ml.), was shaken in hydrogen over 5% palladised charcoal, water (10 ml. portions) being added from time to time to keep the peptide in solution. When absorption was complete, the mixture was heated on the steam-bath for a few minutes and filtered hot. Evaporation of the filtrate gave 2·47 g. (89%) of chromatographically pure L-leucylglycylglycine, $[\alpha]_D^{20}$ +57·3° (*c* 5·01 in water); recrystallisation from aqueous propan-2-ol gave 1·47 g. (53%), $[\alpha]_D^{21}$ +57·2° (Schott *et al.*[14] give $[\alpha]_D^{25}$ +57·7°). The crude tripeptide (1·0000 g.) was heated on a steam-bath for 24 hr. with constant-boiling hydrochloric acid (9 ml.) in a previously heat-treated 10 ml. graduated flask fitted with a ground-in double-surface condenser, then cooled to room temperature. The volume was made up to 10 ml. with constant-boiling hydrochloric acid; the resulting solution had $[\alpha]_D^{19}$ +1·76°; a similarly treated mixture of L-leucine (0·5348 g.) and glycine (0·6121 g.) had $[\alpha]_D^{17}$ +1·73°. Hydrolysis of the peptide to L-leucine and glycine was shown by paper chromatography to be complete.

*N-Benzyloxycarbonyl-*DL*-methionylglycylglycine Benzyl Ester.*—*N*-Benzyloxycarbonyl-DL-methionine [23] (2·83 g.) and glycylglycine benzyl ester toluene-*p*-sulphonate (3·94 g.) were coupled in pyridine (7 ml.) by using bis-*o*-phenylene pyrophosphite (3·23 g.). Recrystallisation of the crude product (3·47 g., 71%) from aqueous ethanol gave the *peptide ester* (2·85 g., 59%), m. p. 115·5—117° (Found: C, 59·4; H, 5·7; N, 8·6. $C_{24}H_{29}O_6N_3S$ requires C, 59·1; H, 6·0; N, 8·6%).

*N-Benzyloxycarbonyl-*L*-tyrosylglycylglycine Benzyl Ester.*—*N*-Benzyloxycarbonyl-L-tyrosine [13] (0·75 g.) and glycylglycine benzyl ester toluene-*p*-sulphonate (0·95 g.) were coupled in pyridine (2 ml.) by using bis-*o*-phenylene pyrophosphite (0·81 g.). The crude product (0·98 g., 79%), m. p. 80—88°, recrystallised from ethyl acetate–light petroleum and from aqueous ethanol, yielding the peptide ester (0·31 g., 25%), m. p. 136°, $[\alpha]_D^{18}$ −8·5° (*c* 1·40 in acetone) (Morris [12] gives m. p. 132—133°, $[\alpha]_D^{16}$ −8·5°).

[20] Lautsch and Kraege, *Chem. Ber.*, 1956, **89**, 737.
[21] Harington and Mead, *Biochem. J.*, 1936, **30**, 1598.
[22] Bergmann, Zervas, and Fruton, *J. Biol. Chem.*, 1936, **115**, 593.
[23] Dekker and Fruton, *ibid.*, 1948, **173**, 471.

N-Benzyloxycarbonylglycyl-L-leucylglycine Benzyl Ester.—(i) *N*-Benzyloxycarbonylglycyl-L-leucine (3·23 g.) and glycine benzyl ester toluene-*p*-sulphonate (3·37 g.) were coupled, in pyridine (7 ml.), by the " standard " procedure, with bis-*o*-phenylene pyrophosphite (3·23 g.). The crude product, isolated with ethyl acetate, solidified (3·26 g., 70%) on treatment with ethyl acetate–light petroleum and had m. p. 122—125°, $[\alpha]_D^{18\cdot5}$ −14·6° (*c* 2·00 in ethanol). Recrystallisation from aqueous ethanol, followed by washing with N-sodium hydrogen carbonate, N-hydrochloric acid and water and two further recrystallisations, gave 1·76 g. (38%), m. p. 127—128°, $[\alpha]_D^{16\cdot5}$ −15·4° (*c* 2·00 in ethanol). This material (1·52 g.) was hydrogenolysed as usual in aqueous t-butyl alcohol over palladised charcoal; the product (0·63 g., 80%) had $[\alpha]_D^{17\cdot5}$ −19·3° (*c* 2·50 in water), indicating it to be about 55% racemised (Bergmann *et al.*[24] give $[\alpha]_D^{24}$ −41·2° for pure glycyl-L-leucylglycine).

(ii) A similar coupling, carried out by the " amide " procedure, gave a crude product (3·85 g., 82%) with m. p. 92—94°, $[\alpha]_D^{18\cdot5}$ −8·8° (*c* 2·01 in ethanol). This was recrystallised once from aqueous ethanol, washed with N-sodium hydrogen carbonate, N-hydrochloric acid, and water, and then fractionally crystallised from aqueous ethanol, affording much extensively racemised material (1·51 g., 32%), m. p. 128—130°, $[\alpha]_D^{17\cdot5}$ + 2·4° (*c* 2·00 in ethanol), and a little optically pure *peptide ester* (0·36 g., 8%), m. p. 102—104°, $[\alpha]_D^{17\cdot5}$ −31·8° (*c* 2·00 in ethanol) (Found: C, 63·9; H, 6·6; N, 8·9. $C_{25}H_{31}O_6N_3$ requires C, 63·9; H, 6·7; N, 9·0%).

N-Phthaloylglycyl-L-tyrosylglycine Benzyl Ester.—*N*-Phthaloylglycyl-L-tyrosine (0·368 g.) and glycine benzyl ester toluene-*p*-sulphonate (0·377 g.) were coupled in pyridine (1·5 ml.) with bis-*o*-phenylene pyrophosphite (0·300 g.). The crude product (0·39 g., 76%), m. p. 113—118°, was thrice recrystallised from aqueous ethanol, once from aqueous 2-ethoxyethanol, and once from ethyl acetate–light petroleum, giving the partially racemised *peptide ester* (0·07 g., 14%), m. p. 167—169°, $[\alpha]_D^{20}$ +14·6° (*c* 0·65 in 2-ethoxyethanol) (Found: C, 64·4; H, 4·9; N, 8·2. $C_{28}H_{25}O_7N_3$ requires C, 65·2; H, 4·9; N, 8·2%); acid hydrolysis gave a product from which 10% of DL-tyrosine was isolated. Neither the yield nor the quality of the product was improved by using the " amide " coupling procedure.

N-Benzyloxycarbonyldiglycyl-L-leucine Benzyl Ester.—*N*-Benzyloxycarbonylglycylglycine [13] (7·98 g.) and L-leucine benzyl ester toluene-*p*-sulphonate (11·80 g.) were coupled in pyridine (21 ml.) with bis-*o*-phenylene pyrophosphite (9·70 g.). The product, isolated with ethyl acetate, was a yellow oil which crystallised on trituration with ethyl acetate–light petroleum; this was suspended in boiling ether (250 ml.) and precipitated with light petroleum. The solid (11·07 g., 79%), m. p. 91—92°, recrystallised from ethyl acetate–light petroleum, giving the pure *peptide ester* (9·86 g., 70%), m. p. 93—94°, $[\alpha]_D^{23\cdot5}$ 0·0° (*c* 2·00 in chloroform) (Found: C, 63·9; H, 6·6; N, 8·9. $C_{25}H_{31}O_6N_3$ requires C, 63·9; H, 6·7; N, 9·0%).

This ester (9·10 g.) in t-butyl alcohol (170 ml.) and water (30 ml.), was shaken in hydrogen over 5% palladised charcoal for 34 hr. Working up as usual gave crude diglycyl-L-leucine (4·15 g., 81%), $[\alpha]_D^{18}$ −29·9° (*c* 2·01 in water), which crystallised from water as the *monohydrate*, m. p. 217° (decomp.), $[\alpha]_D^{19}$ −29·9° (*c* 2·00 in water) (Found: C, 46·3, 46·5; H, 7·9, 7·9; N, 16·0, 16·2. $C_{10}H_{19}O_4N_3,H_2O$ requires C, 45·6; H, 8·0; N, 16·0%) (Fruton *et al.*[25] give $[\alpha]_D^{26}$ −28·0° for the anhydrous tripeptide). The crude tripeptide monohydrate (1·0735 g.) was hydrolysed with constant-boiling hydrochloric acid as described for leucylglycylglycine; the hydrolysate, made up to 10 ml., had α_D^{17} +1·76°.

N-Benzyloxycarbonyldiglycyl-DL-methionine Benzyl Ester.—*N*-Benzyloxycarbonylglycylglycine [13] (5·32 g.) and DL-methionine benzyl ester toluene-*p*-sulphonate (8·23 g.) were coupled in pyridine (10 ml.) with bis-*o*-phenylene pyrophosphite (7·35 g.). The gummy product, isolated with ethyl acetate, crystallised on addition of light petroleum to a concentrated solution in ethyl acetate. Recrystallisation of this crude product (6·29 g., 65%) from ethyl acetate–light petroleum gave the pure *peptide ester* (3·90 g., 40%), m. p. 92—94° (Found: C, 58·8; H, 5·8; N, 8·5; S, 6·4. $C_{24}H_{29}O_6N_3S$ requires C, 59·1; H, 6·0; N, 8·6; S, 6·6%).

N-Benzyloxycarbonyldiglycyl-DL-phenylalanine Benzyl Ester.—*N*-Benzyloxycarbonylglycylglycine [13] (2·66 g.) and DL-phenylalanine benzyl ester toluene-*p*-sulphonate (4·27 g.) were coupled in pyridine (10 ml.) with bis-*o*-phenylene pyrophosphite (3·23 g.). The crude product, isolated with ethyl acetate, crystallised when rubbed with light petroleum. The solid (4·12 g., 82%), m. p. 101—103°, recrystallised from aqueous ethanol, giving the *peptide ester* (3·52 g., 70%), m. p. 113—113·5° (Found: C, 67·0; H, 5·7; N, 8·3. $C_{28}H_{29}O_6N_3$ requires C, 66·8;

[24] Bergmann, Zervas, and Fruton, *J. Biol. Chem.*, 1935, **111**, 225.
[25] Fruton, Smith, and Driscoll, *ibid.*, 1948, **173**, 457.

H, 5·8; N, 8·3%). Use of the benzyl ester hydrochloride instead of the toluene-*p*-sulphonate in this preparation gave a poorer yield (56%).

*N-Benzyloxycarbonyldiglycyl-*L*-tyrosine Benzyl Ester.*—*N*-Benzyloxycarbonylglycylglycine [13] (5·32 g.) and L-tyrosine benzyl ester toluene-*p*-sulphonate (8·87 g.) were coupled in pyridine (13 ml.) with bis-*o*-phenylene pyrophosphite (7·06 g.). The crude product (7·88 g., 76%), m. p. 139—141°, recrystallised several times from aqueous methanol, gave the pure tripeptide ester (4·71 g., 45%), m. p. 161°, $[\alpha]_D^{19}$ +12·8° (*c* 2·00 in dioxan) (Morris [12] gives m. p. 161—162°, $[\alpha]_D^{18}$ +13·7°).

N-Benzyloxycarbonyltriglycylglycine Benzyl Ester.—*N*-Benzyloxycarbonylglycylglycine [13] (2·66 g.) and glycylglycine benzyl ester toluene-*p*-sulphonate (3·95 g.) were coupled in pyridine (10 ml.) with bis-*o*-phenylene pyrophosphite (3·23 g.). Recrystallisation of the crude product (3·90 g., 83%), m. p. 193—195°, from aqueous pyridine gave the pure *peptide ester* (3·29 g., 70%), m. p. 199—200° (Found: C, 58·8; H, 5·7; N, 11·8. $C_{23}H_{26}O_7N_4$ requires C, 58·7; H, 5·6; N, 11·9%).

*N-Benzyloxycarbonylglycyl-*L*-phenylalanylglycine Ethyl Ester.*—*N*-Benzyloxycarbonylglycyl-L-phenylalanine (1·42 g.), redistilled glycine ethyl ester (0·41 g.), and bis-*o*-phenylene pyrophosphite (1·29 g.), in diethyl phosphite (5 ml.), were heated on a steam-bath for 30 min. The mixture was cooled and treated with water (20 ml.). The precipitated oil was dissolved in ethyl acetate and washed with N-hydrochloric acid, N-sodium hydrogen carbonate, and water, dried, and recovered. Addition of water to a concentrated solution in ethanol gave the extensively racemised peptide ester (0·77 g., 44%), m. p. 113—118°, $[\alpha]_D^{18·5}$ −1·6° (*c* 2·00 in ethanol); recrystallisation from aqueous ethanol raised the m. p. to 123—124° (Found: N, 9·8. Calc. for $C_{23}H_{27}O_6N_3$: N, 9·5%) (Sheehan and Hess [9] give m. p. 118—119°, $[\alpha]_D^{27}$ −13·5°).

We thank the Government of Jamaica for a maintenance grant (to J. H. H. M.) and Mr. V. Manohin for the microanalyses.

MANCHESTER COLLEGE OF SCIENCE AND TECHNOLOGY,
MANCHESTER, 1.

[*Received, April* 30*th*, 1959.]

---

724. *Some* NN-*Di*-2-*chloroalkyl Derivatives of Carboxyamides and Sulphonamides.*

by W. C. J. Ross and J. G. WILSON.

A number of *NN*-di-2-chloroalkyl-carboxyamides and -sulphonamides have been prepared for testing as cytotoxic agents. The mechanism of the acid-catalysed rearrangement of the carboxyamides to 2-acyloxyethyl-2′-chloroethylammonium chlorides is discussed.

IN the search for chemotherapeutic agents which could be converted by enzymic action into more potent compounds [1] attention has recently turned towards di-2-chloroalkylamides which on hydrolysis of the amide linkage would be expected to give tumour-growth inhibitory di-2-chloroalkylamines.[2] A certain level of chemical reactivity of the chlorine atom is necessary for biological activity [3] and it is unlikely that this is reached in the parent amides. Friedman and Seligman [4] and Arnold *et al.*[5] have examined various halogenoalkylphosphoramides which are presumed to release active halogenoalkylamines *in vivo*. It is probable that certain cytotoxic *NN*-di-2-chloroalkylurethanes owe their activity [6] to

[1] Everett and Ross, *J.*, 1949, p. 1972; Danielli, *Nature*, 1952, **170**, 862; *idem*, "Ciba Foundation Symposium on Leukaemia Research," 1954, London, p. 263; Danielli and Hebborn, *Biochem. Pharm.*, 1958, **1**, 19; Ross, *Acta Unio Internat. contra Cancrum*, 1954, **10**, 159; Ross, Warwick, and Roberts, *J.*, 1955, p. 3110; Ross and Warwick, *J.*, 1956, p. 1364.

[2] Peczenik, *Brit. J. Cancer*, 1952, **6**, 262; Haddow, "British Empire Cancer Campaign Report," 1957, London, Pt. II, p. 41.

[3] Ross, *Adv. Cancer Res.*, 1953, **1**, 397.

[4] Friedman and Seligman, *J. Amer. Chem. Soc.*, 1954, **76**, 655, 658.

[5] Arnold, Bourseaux, and Brock, *Nature*, 1958, **181**, 931.

[6] Haddow (unpublished results), see also Skipper, Bryan, Riser, Welty, and Stelzenmuller, *J. Nat. Cancer Inst.*, 1948, **9**, 77.

the similar release of " nitrogen-mustard "-like compounds since tumour-inhibitory activity is observed in the di-2-chloroethyl derivative (I) but not in the monofunctional analogue (II) [7]—this requirement is characteristic of growth-retarding halogenoalkylamines.[8]

(I) $EtO{\cdot}CO{\cdot}N(CH_2{\cdot}CH_2Cl)_2$ $EtO{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2Cl$ (II)

The present paper describes the preparation and properties of some *NN*-di-2-chloroalkyl derivatives of aliphatic and aromatic carboxyamides and also of some sulphonamides.

Jones and Wilson [9] prepared *NN*-di-2-chloroethylbenzamide by the Schotten–Baumann technique and more recently Preussmann [10] has reported the preparation of compounds alleged to be *N*-formyl-, *N*-acetyl-, *N*-trichloroacetyl-, and *N*-benzoyl-di-2-chloroethylamine (but see below). The formyl derivative was obtained by the action of thionyl chloride on *NN*-di-2-hydroxyethylformamide whilst the other amides were prepared from di-2-chloroethylamine and the appropriate acid chloride in the presence of triethylamine in an inert solvent.

The latter method has proved satisfactory for the preparation of *NN*-2-chloroethylamides of *o*-, and *p*-nitrobenzoic acid, 3 : 5-dinitrobenzoic acid, and terephthalic acid. Attempts to prepare di-2-chloroethylbenzamide (III; R = Ph) gave 2-benzoyloxyethyl-2′-chloroethylammonium chloride (IV; R = Ph), which Jones and Wilson [9] had previously obtained in small amounts during the recrystallisation of the benzamide (III; R = Ph) and which Mann [11] had earlier obtained and described as di-2-chloroethylamine benzoate:

$$\underset{\text{(III)}}{RCO{\cdot}N(CH_2{\cdot}CH_2Cl)_2} \xrightarrow{H_2O} \underset{\text{(IV)}}{RCO_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH(HCl){\cdot}CH_2{\cdot}CH_2Cl} \qquad \underset{\text{(V)}}{HO_2C{\cdot}X{\cdot}CO{\cdot}N(CH_2{\cdot}CH_2Cl)_2}$$

The amide (III; R = Ph), which was readily obtained by the Schotten–Baumann technique, slowly rearranged in acetone–ether or acetone–light petroleum giving the benzoyloxyethyl derivative. Preussmann's product is clearly impure rearranged material (IV; R = Ph) and not the benzamide as claimed.

All attempts to obtain stable *NN*-di-2-chloroethyl-amides of *p*-anisic, *p*-toluic, *p*-chlorobenzoic, *p*-bromobenzoic, phenylacetic, and cinnamic acids were unsuccessful. On chromatographic purification of the products one obtained oils which slowly deposited the acyloxethylammonium chloride. Succinic anhydride, maleic anhydride, and phthalic anhydride with di-2-chloroethylamine gave the monoamides (V).

NN-Di-2-chloroethyl-amides of the aliphatic acids were oils which could be distilled under reduced pressure with only slight decomposition, with the exception of the acrylamide which polymerised. The distilled amides slowly rearranged giving acyloxyethyl derivatives of structure (IV). Preussmann [10] indicates that his acetamido-compound slowly crystallised—it is obvious that the crystals which separated must have been those of the rearranged product.

The rearrangement of all the *NN*-di-2-chloroethyl-amides could be accelerated by dissolution in acetone containing a few drops of concentrated hydrochloric acid. In most cases the hydrochloride of the acyloxyethyl derivative crystallised within 2—3 days.

Acylation of 2′-acyloxyethyl-2-chloroethylamines followed by acid-induced rearrangement of the products gave bis-2-acyloxyethylamines. In this way symmetrically acylated derivatives such as bis-2-acetoxy- (VI; R = Me), bis-2-benzoyloxy- (VI; R = Ph), and bis-2-*p*-methoxybenzoyloxyethylammonium (VI; R = *p*-$MeOC_6H_4$) chlorides and one unsymmetrical derivative, 2-*p*-bromobenzoyloxyethyl-2′-*p*-nitrobenzoylethylammonium chloride (VII) were obtained.

(VI) $(R{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2)_2NH{\cdot}HCl$ (VII) $BrC_6H_4{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH(HCl){\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}C_6H_4{\cdot}NO_2$

[7] Bergel, Haddow, and Hopwood, personal communication.
[8] Haddow, Kon, and Ross, *Nature*, 1948, **162**, 824.
[9] Jones and Wilson, *J.*, 1949, p. 547.
[10] Preussmann, *Arzneimittelforschung*, 1958, **8**, 9.
[11] Mann, *J.*, 1934, p. 464.

XUM

TABLE 1. *Amides* $RCO\cdot N(CH_2\cdot CH_2Cl)_2$.

R	B. p. or M. p.	Form	Solvent [1]	Formula	Found (%) C	H	N	Required (%) C	H	N	Method	Yield (%)
Me	122—126°/1 mm.[2]	Oil		$C_6H_{11}ONCl_2$	39·1	6·0	7·6	39·4	5·4	7·4	i	73
CH_2Cl	148—149/0·8 mm.[3]	Oil		$C_6H_{10}ONCl_3$	33·0	4·6	6·4	32·2	4·7	6·3	i	57
CH_2F	137—140/1·2 mm.	Oil		$C_6H_{10}ONCl_2F$	36·0	5·3	6·7	35·6	5·0	6·9	i	77
CCl_3	146—148/0·01 mm.	Pale yellow oil		$C_6H_8ONCl_5$	25·0	2·8	4·9	25·7	3·0	4·9	i	87
CF_3	63/0·35 mm.	Oil		$C_6H_8ONCl_2F_3$	30·0	3·5	5·8	30·3	3·4	5·8	i	70
Ph	49	Needles	A	$C_{11}H_{13}ONCl_2$	53·7	5·3	5·7	53·7	5·3	5·7	ii	72
$2\text{-}NO_2\cdot C_6H_4$	62—64	Pale yellow prisms	A	$C_{11}H_{12}O_3N_2Cl_2$	45·2	4·4	9·5	45·4	4·1	9·6	*	38
$4\text{-}NO_2\cdot C_6H_4$	94—96	Pale yellow prisms	B–C	$C_{11}H_{12}O_3N_2Cl_2$	45·6	4·3	9·7	45·4	4·1	9·6	i	79
$3,5\text{-}(NO_2)_2C_6H_3$	116	Pale yellow prisms	B–C	$C_{11}H_{11}O_5N_3Cl_2$	39·4	3·6	12·3	39·3	3·3	12·5	i	78
$4\text{-}NO_2\cdot C_6H_4\cdot CH_2$	82—83	Yellow prisms	D–E	$C_{12}H_{14}O_3N_2Cl_2$	47·5	4·7	9·5	47·2	4·6	9·2	ii	20
$1,2\text{-}C_6H_4$	—	Viscous oil		$C_{16}H_{20}O_2N_2Cl_4$	46·5	4·9	6·6	46·4	4·8	6·8	i	90
$1,4\text{-}C_6H_4$ [4]	176—177	Prisms	B–E	$C_{16}H_{20}O_2N_2Cl_4$	46·6	5·1	6·7	46·4	4·8	6·8	i	66
$2\text{-}C_6H_4\cdot CO_2H$	141	Prisms	B–F	$C_{12}H_{13}O_3NCl_2$	49·8	4·6	4·9	49·7	4·5	4·8	*	78
$[CH_2]_2\cdot CO_2H$	77—78	Needles	D–F	$C_8H_{13}O_3NCl_2$	39·5	5·8	5·5	39·7	5·4	5·8	*	80
$CH{=}CH\cdot CO_2H$	102·5	Prisms	B	$C_8H_{11}O_3NCl_2$	39·8	4·9	5·9	40·0	4·6	5·8	*	85

[1] Solvents used for crystallisation are: A, light petroleum (b. p. 80—100°); B, chloroform; C, ether; D, benzene; E, light petroleum (b. p. 60—80°); F, light petroleum (b. p. 40—60°). [2] Childs *et al.* (ref. 19) give b. p. 130—135°/0·2 mm. and Preussmann (ref. 10), b. p. 134—138°/4 mm. [3] Childs *et al.* give b. p. 160—164°/0·2 mm. [4] This compound separated as crystals from the initial mixture. * See experimental section.

TABLE 2. *Amine hydrochlorides* $RCO_2\cdot CH_2\cdot CH_2\cdot NH\cdot CH_2\cdot CH_2Cl,HCl$ *and the corresponding picrates.*

R	M. p.	Form	Solvents [1]	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl	Yield (%)
Me	100—101°	Plates	A–B	$C_6H_{13}O_2NCl_2$	35·8	6·4	7·0		35·6	6·4	6·9		25
CH_2Cl	93	Needles	A	$C_6H_{12}O_2NCl_3$	29·8	5·2	6·0		30·4	5·1	5·9		32
CH_2F	86—88	Plates	A	$C_6H_{12}O_2NCl_2F$	32·8	5·2	6·4		32·8	5·4	6·4		15
CH_2Ph	105—106	Plates	A	$C_{12}H_{17}O_2NCl_2$	51·8	6·2	5·1		51·8	6·1	5·2		70
$4\text{-}NO_2\cdot C_6H_4\cdot CH_2$	122—124	Needles	A	$C_{12}H_{16}O_4N_2Cl_2$	44·8	5·1	8·6		44·6	5·0	8·7		47
(picrate)	86—88	Plates	C–E	$C_{18}H_{16}O_{11}N_5Cl$			13·1	6·7			13·6	6·9	
Ph	129—131	Plates	A	$C_{11}H_{15}O_2NCl_2$	50·2	5·9	5·3		50·0	5·7	5·3		48
(picrate)	181·5	Needles	C	$C_{17}H_{17}O_9N_4Cl$			12·4	8·1			12·3	7·8	
$4\text{-}Me\cdot C_6H_4$	150	Needles	A	$C_{12}H_{17}O_2NCl_2$	52·1	6·4	5·2		51·8	6·1	5·2		66
(picrate)	174—176	Prisms	C	$C_{18}H_{19}O_9N_4Cl$			11·8	7·6			11·9	7·5	
$4\text{-}MeO\cdot C_6H_4$	126	Plates	A	$C_{12}H_{17}O_3NCl_2$	48·9	5·9	4·8		49·0	5·8	4·8		64
(picrate)	163	Prisms	C	$C_{18}H_{19}O_{10}N_4Cl$			11·2	6·9			11·5	7·3	
$4\text{-}Cl\cdot C_6H_4$	129—131	Needles	A	$C_{11}H_{14}O_2NCl_3$	44·3	4·6	4·6		44·2	4·7	4·7		43
(picrate)	168—169	Needles	C	$C_{17}H_{16}O_9N_4Cl_2$			11·4	14·2			11·4	14·5	
$4\text{-}Br\cdot C_6H_4$	151—153	Needles	A–D	$C_{11}H_{14}O_2NCl_2Br$	38·8	4·4	4·0		38·5	4·1	4·1		55
(picrate)	174	Prisms	C	$C_{17}H_{16}O_9N_4ClBr$			10·1	6·5			10·5	6·6	
$4\text{-}NO_2\cdot C_6H_4$	191—193	Yellow needles	A–D	$C_{11}H_{14}O_4N_2Cl_2$	42·8	4·7	9·2		42·7	4·7	9·4		80
(picrate)	171	Needles	C	$C_{17}H_{16}O_{11}N_5Cl$			13·7	6·8			13·9	7·1	
$3,5\text{-}(NO_2)_2C_6H_3$	170—171	Yellow needles	A	$C_{11}H_{13}O_6N_3Cl_2$	37·7	3·8	11·9		37·4	3·7	11·8		35
(picrate)	192—193	Needles	C	$C_{17}H_{15}O_{13}N_6Cl$			15·6	6·3			15·8	6·5	
$Ph\cdot CH{=}CH$	120	Needles	A	$C_{13}H_{17}O_2NCl_2$	54·0	6·0	4·8		53·8	5·9	4·8		21
(dipicrate)	147	Prisms	C	$C_{25}H_{22}O_{16}N_7Cl$			13·7	5·0			13·8	5·0	
$1,4\text{-}C_6H_4$	225	Prisms	A–D	$C_{16}H_{24}O_4N_2Cl_4$	42·8	5·4	6·4		42·7	5·3	6·2		92
(dipicrate)	174	Prisms	C	$C_{28}H_{26}O_{18}N_8Cl_2$			13·4	8·6			13·8	8·8	
$[CH_2]_2\cdot CO_2H$	104—105	Plates	A–D	$C_8H_{15}O_4NCl_2$	37·1	6·1	5·4		36·9	5·8	5·4		70
$CH{=}CH\cdot CO_2H$	141—143	Plates	D–F	$C_8H_{13}O_4NCl_2$	37·2	4·8	5·4		37·2	5·0	5·4		67

[1] Solvents used for crystallisation are: A, acetone; B, light petroleum (b. p. 60—80°); C, ethanol; D, methanol; E, water; F, ether.

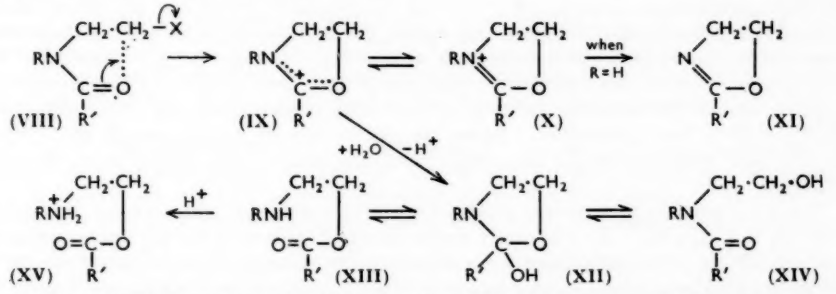
XUM

The di-2-chloroethyl-amides now prepared are listed in Table 1 and the acyloxyethyl-chloroethylammonium chlorides in Table 2.

Dr. R. Wade drew our attention to the greater stability towards rearrangement of certain *NN*-di-2-chloropropyl-amides and accordingly *NN*-di-2-chloropropylbenzamide was examined. It was stable under conditions which converted the corresponding di-2-chloroethyl-amide into 2-benzoyloxyethyl-2′-chloroethylammonium chloride.

NN-Di-2-chloroethyl-amides of several sulphonic acids were readily obtained from the appropriate acid chloride and di-2-chloroethylamine in pyridine. These amides, which were quite stable and showed no tendency to undergo acid-catalysed rearrangement, are listed in Table 3.

The rearrangement of *NN*-di-2-chloroethyl-amides, which involves intramolecular acyl-group migration, can be depicted as below:



The acid-catalysed formation of the bridged cation (IX) which can be stabilised by resonance with the quaternary ion (X) is a special instance of the first stage suggested [12] for migrations in substituted ethane systems. The scheme is consistent with the formation of phenyloxazoline (XI; R′ = Ph) from *N*-2-bromoethylbenzamide (VIII; R = H, R′ = Ph, X = Br) which occurs [13] when the halide is rapidly dissolved in boiling water. In this

TABLE 3. *Sulphonamides* $RSO_2 \cdot N(CH_2 \cdot CH_2Cl)_2$.

R	M. p.	Form	Solvent [1]	Formula	Found (%) / Required (%) C	H	N	Yield (%)
Me	67° [2]	Needles	A	$C_5H_{11}O_2NCl_2S$	27·7	5·1	6·5	70
					27·3	5·0	6·4	
Ph	45—46	Prisms	A	$C_{10}H_{13}O_2NCl_2S$	42·6	4·8	4·6	62
					42·6	4·6	5·0	
4-Me·C_6H_4	46 [3]	Prisms	A	$C_{11}H_{15}O_2NCl_2S$	44·6	5·2	4·5	65
					44·7	5·1	4·7	
4-MeO·C_6H_4	76	Prisms	B	$C_{11}H_{15}O_3NCl_2S$	42·5	5·1	4·6	67
					42·3	4·8	4·5	
4-ClC_6H_4	91	Needles	B	$C_{10}H_{12}O_2NCl_3S$	37·7	4·0	4·6	76
					37·9	3·8	4·4	
4-Br·C_6H_4	81·5	Prisms	B	$C_{10}H_{12}O_2NBrCl_2S$	33·3	3·1	4·1	71
					33·2	3·3	3·9	
4-AcNH·C_6H_4	111 [3]	Needles	A–C	$C_{12}H_{16}O_3N_2Cl_2S$	42·2	4·8	8·2	15
					42·5	4·7	8·3	
4-NO_2·C_6H_4	124	Prisms	B	$C_{10}H_{12}O_4N_2Cl_2S$	36·7	3·7	9·0	61
					36·7	3·7	8·6	

[1] Solvents used for crystallisation are: A, methanol; B, ethanol; C, water. [2] Preussmann (ref. 10) gives 76—78°. [3] These agree with Preussmann's values (ref. 10).

instance the cation (X) will lose a proton to give a weakly basic oxazoline, but with *N*-2-chloroethyl-*N*-methylbenzamide and the di-2-chloroethyl-amide (VIII; R = Me, R′ = Ph) such stabilisation is not possible.

[12] Cram, "Steric Effects in Organic Chemistry," ed. M. S. Newman, John Wiley and Sons, Ltd., New York, 1956, p. 290.
[13] Gabriel and Heymann, *Ber.*, 1890, **23**, 2497.

Markwald and Frobenius [14] have shown that the compound (VIII; R = Me, R′ = Ph, X = Cl) undergoes rearrangement similar to that now being discussed giving 2-methylaminoethyl benzoate.

Ortho-acid derivatives (XII) postulated in this scheme and also regarded [15] as intermediates in the N $\rightleftharpoons$ O acyl-group migration (XIII $\rightleftharpoons$ XIV) have been shown [16] to exist by the synthesis of the magnesium salt of *threo*-2-hydroxy-3,4-dimethyl-2,5-diphenyloxazolidine. The equilibrium (XIII $\rightleftharpoons$ XII $\rightleftharpoons$ XIV) is displaced to the left by acids and to the right by bases.[17] This is consistent with (XIV) being the most stable structure, the equilibrium only being displaced in favour of (XIII) when this is stabilised in acid solution by the addition of a proton giving (XV) from which (XII) cannot be derived. Only catalytic amounts of acid are required for complete rearrangement of compounds (VIII) since acid is produced as (XIII) is formed and the amount is sufficient to ensure complete conversion.

The greater stability of 2-chloroethyl-amides (VIII) when R′ is an electron-attracting group—as in the various nitrobenzoic acid derivatives—is expected if formation of the bridged cation (IX) is involved for in such compounds the mobility of electrons in the carbonyl bond in the direction indicated will be reduced thus hindering the depicted ring closure by O–C bond formation. Again the slower rate of rearrangement of 2-chloropropyl-amides would be due to the relative steric hindrance to the formation of this same O–C bond.

It was not possible to determine the hydrolysis rates of the chlorine atoms in the amides (VIII; R = $CH_2 \cdot CH_2Cl$, X = Cl) since under the conditions used for the measurement of these rates [18] the *NN*-di-2-chloroethyl-amides rapidly underwent prior rearrangement to the esters (XIII).

Most of the *NN*-di-2-chloroethyl-amides (III) and their rearrangement products (IV) have been tested for effect on the growth of the transplanted Walker rat carcinoma. The derivatives from succinic (XVI) and phthalic acid (XVII) showed activity of a low order but the remainder were inactive.

(XVI) $HO_2C \cdot CH_2 \cdot CH_2 \cdot CO \cdot N(CH_2 \cdot CH_2Cl)_2$ o-$HO_2C \cdot C_6H_4 \cdot CO \cdot N(CH_2 \cdot CH_2Cl)_2$ (XVII)

The original hope that di-2-chloroethylamine would be released by hydrolysis *in vivo* of the amide linkage now seems unlikely in view of the rearrangement to the ester (IV).

Experimental

Preparation of Di-2-chloroethyl-amides.—Method (i). The unpurified acid chloride [prepared by action of thionyl chloride on the acid (0·04 mol.)] in chloroform was added slowly to a stirred solution of di-2-chloroethylamine prepared from the hydrochloride (0·045 mol.) and triethylamine (0·045 mol.) in chloroform. Stirring was continued for 30 min. and the mixture was then washed with water, 2N-hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and finally again with water. Distillation of the solvent from the dried (magnesium or sodium sulphate) solution afforded thick oils which solidified on cooling in the case of *p*-nitro- and 3,5-dinitro-benzamide. The other amides prepared by this method were obtained as viscous oils which were rearranged to the ester hydrochlorides on storage or attempted crystallisation from hydroxylic solvents. In the attempted preparation of amides from *p*-nitrophenylacetic acid, *p*-anisic acid, and *p*-toluic acid, the acyloxyethylammonium chlorides separated from the chloroform solutions of the initial product. The tendency to rearrange was clearly enhanced by washing with dilute hydrochloric acid for when this step was omitted the separation of the crystalline hydrochloride was considerably delayed, or even prevented. The general method

[14] Markwald and Frobenius, *Ber.*, 1901, **34**, 3544.
[15] Phillips and Baltzly, *J. Amer. Chem. Soc.*, 1947, **69**, 200.
[16] Koczka and Fodor, *Acta Chim. Hung.*, 1957, **13**, 6.
[17] Reasenberg and Goldberg, *J. Amer. Chem. Soc.*, 1945, **67**, 933.
[18] Ross, *J.*, 1949, p. 183.

was satisfactory for the preparation of trichloro- and trifluoro-acetamide which showed no tendency to rearrange. Attempted distillation of the acrylamide derivative led to extensive polymerisation.

Childs *et al.*[19] have used a modification of this method in which the acid chloride dissolved in a small volume of chloroform was added simultaneously with alkali to a stirred aqueous suspension of di-2-chloroethylamine so that the mixture remained alkaline. Even when this method was used and the dried chloroform solution was distilled immediately, the amides of acetic, chloroacetic, and fluoroacetic acid were obtained as syrups from which the ester hydrochlorides slowly separated.

Method (ii). A solution of di-2-chloroethylammonium chloride (0·05 mol.) in water (25 ml.) was stirred at 0—5°, and the acid chloride (0·03 mol.) in dry acetone (10 ml.) and aqueous sodium hydroxide (50 ml.; N) were run in simultaneously during 20 min. The rates of addition were adjusted so that the solution remained slightly alkaline. Stirring was continued for a further hour and the product, if solid, was filtered off and washed with aqueous sodium hydrogen carbonate followed by light petroleum (b. p. 40—60°). When the product was an oil it was extracted into chloroform, and the extract washed with water and dried ($MgSO_4$). *NN*-Di-2-chloroethyl-benzamide and -p-nitrophenylacetamide were obtained crystalline by this modification of Jones and Wilson's method [9] whereas the derivatives of other aromatic acids examined were obtained as oils which were converted into the acyloxyethylammonium chlorides as described below.

NN-*Di-2-chloropropylbenzamide.*—This compound, prepared from di-2-chloropropylamine by method (ii) formed large prisms, m. p. 75—77°, from light petroleum (b. p. 60—80°) (Found: C, 56·6; H, 6·0; N, 5·1. $C_{13}H_{17}ONCl_2$ requires C, 56·9; H, 6·2; N, 5·1%). The amide was unchanged when a solution in acetone containing concentrated hydrochloric acid was kept for 1 week.

NN-*Di-2-chloroethyl-*o*-nitrobenzamide.*—*o*-Nitrobenzoyl chloride, prepared by the action of thionyl chloride (13·1 g.) on the acid (16·7 g.) in benzene solution, was added dropwise during 15 min. to a stirred solution of di-2-chloroethylamine [from the hydrochloride (18 g.) and triethylamine (14·2 ml.) in benzene (50 ml.)]. After being stirred for a further hour the mixture was washed with water, and the solvent removed under reduced pressure. A benzene solution of the residue was allowed to percolate through activated alumina which was washed with fresh benzene. Early eluates contained a yellow oil which slowly crystallised. Recrystallisation from a large volume of light petroleum (b. p. 80—100°) gave the amide as large yellow prisms (7·3 g.), m. p. 61—63°. More crude amide (3·8 g.), m. p. 58—61°, was present in the mother liquors. The analytical specimen had m. p. 62—64°.

NN-*Di-2-chloroethyl Derivatives of Phthalamic, Succinamic, and Maleamic Acids.*—The phthalamic and maleamic acid derivatives were obtained in excellent yield by mixing equimolecular amounts of the acid anhydride and di-2-chloroethylamine in dry chloroform; the products separated almost immediately as crystals. To prepare the succinamic acid derivative succinic anhydride was added to a benzene solution of the base at <30°. Subsequent addition of light petroleum (b. p. 60—80°) initiated crystallisation of product which was again obtained in good yield. The derivative could be recrystallised from benzene–light petroleum (b. p. 60—80°) but is was essential to keep the temperature below 40° to prevent separation of non-crystallisable oil.

Attempted Preparation of NN-*Di-2-chloroethyl-*p*-nitrophenylacetamide.*—Before this compound was successfully obtained by method (ii) an attempt was made to prepare it by adding dicyclohexylcarbodi-imide to equimolecular quantities of *p*-nitrophenylacetic acid and di-2-chloroethylamine in tetrahydrofuran; only a small amount of 2-*p*-nitrophenylacetoxyethyl-2′-chloroethylammonium chloride was obtained.

Acid-catalysed Rearrangement of NN-*Di-2-chloroethylamides.*—The compound was dissolved in acetone (about 10 ml. per g.) and a few drops of concentrated hydrochloric acid were added. The acyloxyethylchloroethylammonium chlorides began to crystallise from the solution after 1—5 days and were collected after 2 weeks. They were recrystallised from acetone and when possible were further characterised as the picrates. The rate of rearrangement was slowest when the group R in (II) carried electron-attracting substituents; for example, the 3,5-dinitrobenzoic acid derivative rearranged very slowly—36% being unchanged after 3 weeks. The

[19] Childs, Goldsworthy, Harding, King, Nineham, Norris, Plant, Selton, and Tompsett, *J.*, 1948, p. 2174.

XUM

trichloro- and trifluoro-acetamides and those of *o*-nitrobenzoic acid and phthalamic acid were not rearranged under the above conditions.

Di-2-acetoxyethylammonium Chloride.—To a well-stirred solution of 2-acetóxyethyl-2′-chloroethylammonium chloride (4·5 g.) and triethylamine (5 ml.) in chloroform (20 ml.), acetyl chloride (5 ml.) in chloroform (5 ml.) was added during 10 min. After being stirred for 1 hr. at room temperature the solution was washed with water, dried ($MgSO_4$), and concentrated. The product was dissolved in acetone (10 ml.) to which one drop of concentrated hydrochloric acid had been added. After 18 hr. the rearrangement product (1·2 g.) was collected and recrystallised from acetone. Di-2-acetoxyethylammonium chloride formed plates, m. p. 147—148° undepressed on admixture with an authentic specimen prepared by Mann's method;[11] he gives m. p. 147—149°.

Di-2-benzoyloxyethylammonium Chloride.—2-Benzoyloxyethyl-2′-chloroethylammonium chloride was converted into the oily benzamide by treatment with benzoyl chloride, method (i) or (ii) being used. *Di-2-benzoyloxyethylammonium chloride*, obtained by acid-catalysed rearrangement of the amide, formed small felted needles, m. p. 160° from acetone (Found: C, 62·2; H, 6·1; N, 4·0. $C_{18}H_{20}O_4NCl$ requires C, 61·8; H, 5·7; N, 4·0%). The *picrate* crystallised from ethanol as needles, m. p. 124—125° (Found: C, 52·8; H, 4·4; N, 10·2. $C_{24}H_{22}O_{11}N_4$ requires C, 53·1; H, 4·1; N, 10·3%).

Di-2-p-*methoxybenzoyloxyethylammonium Chloride.*—This compound was similarly prepared; it formed needles, m. p. 165°, from acetone–methanol (Found: C, 58·8; H, 6·2; N, 3·7. $C_{20}H_{24}O_6NCl$ requires C, 58·6; H, 5·9; N, 3·4%). The *picrate* formed golden blades, m. p. 145—147°, from ethanol (Found: C, 51·6; H, 4·7; N, 9·3. $C_{26}H_{26}O_{13}N_4$ requires C, 51·8; H, 4·3; N, 9·3%).

2-p-*Bromobenzoyloxyethyl*-2′-p-*nitrobenzoyloxyethylammonium Chloride.*—*p*-Nitrobenzoylation of 2-*p*-bromobenzoyloxyethyl-2′-chloroethylamine by method (i) gave a product which crystallised from ethanol without rearrangement. It formed prisms, m. p. 98° (Found: C, 47·6; H, 3·8; N, 6·0. $C_{18}H_{16}O_5N_2BrCl$ requires C, 47·4; H, 3·5; N, 6·1%). This amide (5 g.) was dissolved in acetone (20 ml.) containing two drops of concentrated hydrochloric acid, and the rearrangement *product* (2·6 g.) (VII) was collected at intervals during 3 weeks; it formed flattened needles, m. p. 182—183°, from methanol (Found: C, 45·6; H, 4·2; N, 6·4. $C_{18}H_{18}O_6N_2BrCl$ requires C, 45·6; H, 3·8; N, 5·9%). The N-*benzenesulphonyl derivative* was obtained as needles, m. p. 108°, from methanol (Found: C, 49·9; H, 3·7; N, 5·0; $C_{24}H_{21}O_8N_2BrS$ requires C, 49·9; H, 3·6; N, 4·9%).

NN-*Di*-2-*chloroethylsulphonamides.*—The sulphonyl chloride (0·025 mol.) was added to a solution of di-2-chloroethylammonium chloride (0·05 mol.) in pyridine (25 ml.), and the mixture was heated on a steam-bath for 1 hr. and then poured into water. The product was filtered off and washed with water. The sulphonamides were crystallised from ethanol or methanol (Table 3).

This investigation was supported by the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service. The authors thank Professor Haddow, F.R.S., for permission to quote the results of biological tests.

THE CHESTER BEATTY RESEARCH INSTITUTE,
INSTITUTE OF CANCER RESEARCH, ROYAL CANCER HOSPITAL,
FULHAM ROAD, LONDON, S.W.3.

[*Received, May 1st,* 1959.]

XUM

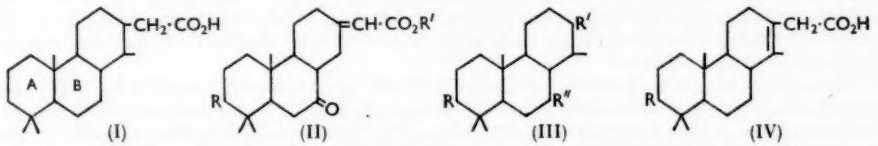
725. *The Oxygen Groups of Cassaic Acid.*

By V. P. Arya and David W. Mathieson.

Dehydrogenation suggests the correctness of formula (II; R = OH, R′ = H) for cassaic acid.

The carbon skeleton of cassaic acid [1,2] was confirmed by preparation of cassanic acid (I) from vouacapenic acid.[3] Cassaic acid has a double bond α to the carboxylic acid, and a keto- and a hydroxyl group, the last two being distributed between rings A and B of the phenanthrene nucleus. Formula (II; R = OH, R′ = H) was put forward as a working hypothesis.[2,4] Its correctness is suggested by our dehydrogenation experiments.

The position of the hydroxyl group has been shown as follows. Ozonolysis of methyl cassate acetate (II; R = OAc, R′ = Me) furnished a diketone (III; R = OAc, R′ = R″ = O) which on Wolff–Kishner reduction yielded perhydro-2-hydroxy-1,1,8,12-tetramethylphenanthrene (III; R = OH, R′ = R″ = H), concomitant hydrolysis of the acetoxy-group taking place. Chromic anhydride–pyridine then smoothly gave the 2-oxo-compound and the position of this oxygen (the original hydroxyl group) was marked by means of the Grignard reagent: dehydrogenation afforded 1,2,8-trimethylphenanthrene.



(I) (II) (III) (IV)

The ketone group of cassaic acid which must therefore be at position 9 or 10 is rather inert since it resisted Clemmensen reduction. Dioxocassenic acid (II; R = O, R′ = H) was therefore reduced under the same conditions, giving 9-oxocassenic acid (II; R = R′ = H), in which a ketone group still survived, this interpretation being supported by the Zimmermann test: Barton and de Mayo [5] showed that this test, characteristic of steroidal 3-ketones, is given also by triterpenes with a ketone group in the same position (not by an 11-, 12-, 16-, or 19-ketone of the β-amyrin series or 7- or 11-ketone of the lanostane group). In the cassaic acid series only a 2- * or 7-ketone gave a colour with the Zimmermann reagent (see Experimental section) and since the acid (II; R = R′ = H) obtained from the Clemmensen reduction above gave a negative Zimmermann test, we felt reasonably certain of the absence of a 2-ketone.† Attempts to synthesise the isomeric 2-oxocassenic acid were unsuccessful. Thus, although cassaic acid was inert to Clemmensen reduction, the Wolff–Kishner procedure gave a hydroxy-acid which showed no absorption above 200 mμ and was presumably the allo-compound (IV; R = OH). Oxidation with chromic anhydride yielded the corresponding 2-oxoallocassenic acid (IV; R = O).

Ozonolysis of the acid (II; R = R′ = H) yielded a dioxo-compound (III; R = H, R′ = R″ = O), which on treatment with methyl-lithium followed by selenium dehydrogenation afforded 1,7,8,9-tetramethylphenanthrene. Formula (II; R = R′ = H) for cassaic acid, is thus confirmed.‡

* Steroidal $C_{(2)}{\equiv}C_{(2)}$ of the perhydrophenanthrene structure.

† Cf. the reduction of 3,7,12-trioxocholanic acid to 7,12-dioxocholanic acid.[6]

‡ During preparation of this manuscript a preliminary note [7] appeared in which much of the stereochemistry and the position of the oxygen atom in ring B have been elegantly demonstrated.

[1] Dalma, *Helv. Chim. Acta*, 1939, **22**, 1497; Ruzicka and Dalma, *ibid.*, p. 1516; 1940, **23**, 753; Ruzicka, Dalma, and Scott, *ibid.*, 1941, **24**, 179E; Ruzicka, Engel, Ronco, and Berse, *ibid.*, 1945, **28**, 1038.

[2] Humber and Taylor, *J.*, 1955, 1044.

[3] King, King, and Uprichard, *J.*, 1958, 3428.

[4] Tondeur, Ph.D. Thesis, Eidgen. Techn. Hochschule, Zurich, 1950.

[5] Barton and de Mayo, *J.*, 1954, 887.

[6] Borsche, *Ber.*, 1919, **52**, 1363.

[7] Turner, Herzog, Morin, and Riebel, *Tetrahedron Letters*, 1959, No. 2, p. 7.

XUM

During our work Professor W. J. Gensler of Boston University kept us informed of his similar findings, partly published already (ref. 9). We are very grateful for such information before publication and for a specimen of 1,7,8,9-tetramethylphenanthrene which he synthesised for the first time.

Ozonolysis of dioxocassenic acid (II; R = O, R′ = H) to give the triketone (III; R = R″ = R‴ = O) has been reported by Engel.[8] We find that the same triketone is also obtained from cassaic acid itself, the 2-hydroxyl group being oxidised. By contrast, a 9-hydroxyl group is inert and the product of ozonolysis of cassaidic acid contains a hydroxyl group: since this product yields a purple colour with the Zimmermann reagent, it is probably the hydroxy-diketone (III; R = R′ = O, R″ = OH). In addition to the differing reactivity of the 2- and the 9-oxygen atom with amalgamated zinc or ozone, it has already been reported [9] that 2- but not 9-ketones react with the Grignard reagent.

Experimental

The bark of *Erythrophleum guineense* (G. Don) came partly from Sierra Leone, and partly from the Belgian Congo. We thank the Colonial Products Council and l'Institut National pour l'Étude Agronomique du Congo Belge (INEAC) for their generous help in supplying botanical material. The bark was extracted essentially as described by Ruzicka, Dalma, and Scott [10] for *Erythrophleum couminga*.

Cassaine Hydrogen Sulphate.—The crude alkaloidal fraction was dissolved in dry ether and, with stirring, 3% sulphuric acid in ether was added at 20° until no further precipitate formed. The mixture was kept at 0° for several hours and the crude precipitate then collected. The yield of cassaine hydrogen sulphate varied in the limits 4—14%. Crystallisation of crude material from methanol gave colourless plates, m. p. 289—290° (decomp.), $[\alpha]_D^{24}$ −96° (in ethanol, *c* 1).

Cassaic Acid.—Cassaine hydrogen sulphate (6 g.) was heated at 100° with 2N-hydrochloric acid (220 ml.). After 2 hr. the oily material which separated initially had become granular (yield, 3·15 g.). Crystallisation from ethanol–ether gave prisms, m. p. 218—220°, $[\alpha]_D^{20}$ −124° (in ethanol, *c* 1·2) (Dalma [1] gives m. p. 203°, $[\alpha]_D^{20}$ −126°), $\nu_{max.}$ (in Nujol mull) 3500 (OH), 2500 (OH), 1710 (C=O), 1678 (CO_2H), 1635 (C=C), 1200 (CO_2H) cm.$^{-1}$. Cassaic acid gave no colour with the Zimmermann reagent.

Cassaic acid formed a p-*phenylphenacyl ester*, m. p. 195—197° (from aqueous ethanol), $[\alpha]_D^{24}$ −108° (in chloroform, *c* 1) (Found: C, 77·6; H, 7·7. $C_{34}H_{40}O_5$ requires C, 77·3; H, 7·6%). Methyl cassate formed an *oxime*, m. p. 108—110° (from ether–light petroleum) (Found: N, 3·7. $C_{21}H_{33}O_4N$ requires N, 3·85°).

Methyl cassate formed a 2,4-*dinitrophenylhydrazone*, orange needles (from ethyl acetate–ethanol), m. p. 145—147°, $\lambda_{max.}$ (main band in ethanol) 361 mμ (log ε 4·3) (Found: C, 61·2; H, 6·7; N, 10·7. $C_{27}H_{36}O_7N_4$ requires C, 61·3; H, 6·8; N, 10·6%).

2-*Acetoxyperhydro*-1,1,8,12-*tetramethyl*-7,9-*dioxophenanthrene* (III) (R = OAc, R′ = R″ = O).—Methyl cassate (695 mg.) in dry chloroform (85 ml.) was treated with 5—6% ozonised oxygen for 90 min. at −20° to −40°. The resulting blue solution was allowed to attain room temperature in 3 hr. and the solvent was then removed. The gummy ozonide (760 mg.) in glacial acetic acid (20 ml.) was treated with powdered zinc (2 g.), shaken for 15 min., then intermittently for 2 hr. Unchanged metal was filtered off and the solvent was removed, being replaced by dilute hydrochloric acid (200 ml.). An ether extract yielded a neutral residue (570 mg.). Crystallisation from ether gave the acetoxy-diketone in plates, m. p. 162·5—164° (Found: C, 71·7; H, 8·8. $C_{20}H_{30}O_4$ requires C, 71·9; H, 9·0%), $\nu_{max.}$ (in bromoform) 1720 (C=O) and 1240 cm.$^{-1}$ (OAc).

The acetoxy-diketone (15 mg.) with N-alcoholic potassium hydroxide to 100° for 2 hr. gave the corresponding hydroxy-diketone, m. p. 173—175° (from ether–light petroleum), $[\alpha]_D^{20}$ −68° (in ethanol, *c* 0·8). Neither the acetoxy- nor the hydroxy-compound gave a colour with the Zimmermann reagent.

[8] Engel, *Helv. Chim. Acta*, 1959, **42**, 131.
[9] Gensler and Sherman, *Chem. and Ind.*, 1959, 223.
[10] Ruzicka, Dalma, and Scott, *Helv. Chim. Acta*, 1941, **24**, 63.

XUM

Perhydro-1,1,8,12-*tetramethyl*-2,7,9-*trioxophenanthrene* (III; R = R′ = R″ = O).—Cassaic acid (200 mg.) in glacial acetic acid (20 ml.) was ozonised as above. The ozonide was decomposed by warm water (~15 ml.), and on working up in the usual fashion a neutral fraction resulted (75 mg.). Crystallisation from ether–light petroleum gave the triketone in needles, m. p. 182—183°, $[\alpha]_D$ −75° (in ethanol, *c* 0·8) (Engel [8] gives m. p. 198·5—200°), $[\alpha]_D^{21}$ −61°) (Found: C, 73·9; H, 8·6. Calc. for $C_{18}H_{26}O_3$: C, 74·5; H, 9·0%).

Passing this material in ether through an alumina column afforded higher-melting material, 197—198·5°, $\lambda_{max.}$ (in ethanol) 289 mμ (log ε 1·81), $\nu_{max.}$ (in bromoform) 1706 cm.$^{-1}$ (C=O) (no OH bands). This change in m. p. probably indicates a change in conformation of the 8-methyl group.

The same triketone was (m. p. and mixed m. p. 182—184°) obtained on ozonolysis of methyl dioxocassenate. It gave a purple colour with the Zimmermann reagent.

Sodium carbonate extracts from purification of the ozonolysis product from cassaic acid were acidified, evaporated to 10—15 ml., then extracted with ether in a liquid–liquid extractor. The ethereal extract was washed with 20% aqueous ammonia and to this solution of ammonium salts was added a concentrated calcium chloride solution till no further precipitate of calcium oxalate was obtained. The isolated calcium oxalate (51 mg.) was then decomposed with dilute sulphuric acid, and the precipitated calcium sulphate centrifuged off. The filtrate was titrated with 0·2N-sodium hydroxide, made just acid with hydrobromic acid, and refluxed with 4-nitrobenzyl bromide (26 mg.) in ethanol (5 ml.) for 1½ hr. The ester which separated crystallised from ethyl alcohol, had m. p. 204° (decomp.) alone or mixed with di-4-nitrobenzyl oxalate.

Perhydro-2-*hydroxy*-1,1,8,12-*tetramethylphenanthrene* (III; R = OH, R′ = R″ = H).—The acetoxy-diketone (200 mg.) was added to redistilled diethylene glycol (10 ml.) in which sodium (100 mg.) had dissolved. Sufficient anhydrous hydrazine was distilled into this to ensure that the reflux temperature was 180°; refluxing was continued at this temperature for 24 hr., then sufficient hydrazine was distilled out to raise the temperature to 210°, a further 24 hours' refluxing being allowed. The cooled mixture was poured into 0·5N-hydrochloric acid and extracted with ether. From this a neutral residue (120 mg.) resulted. This crystallised from ether–light petroleum to give the *product* as prisms, m. p. 147—148°, $[\alpha]_D^{21}$ +28° (in ethanol, *c* 1) (Found: C, 81·6; H, 11·9; O, 6·0. $C_{18}H_{32}O$ requires C, 81·9; H, 12·1; O, 6·1%), $\nu_{max.}$ (KBr disc) 3416 cm.$^{-1}$ (OH) (C=O bands were absent), giving no colour with the Zimmermann reagent.

This product (230 mg.) with chromic anhydride gave (75 mg.) in pyridine (0·75 ml.) a gummy ketone ($\nu_{max.}$ 1703 cm.$^{-1}$), which afforded a positive Zimmermann test.

The crude ketone (210 mg.) in anhydrous ether (50 ml.) was added dropwise to methylmagnesium iodide (from 100 mg. of Mg). After 1 hour's refluxing the mixture was worked up in the usual manner to yield a gummy alcohol (217 mg.). This was heated with selenium (180 mg.) at 340° for 24 hr.; the mixture was extracted with ether, and the extract filtered through a short column of alumina. The eluate, with picric acid, yielded a picrate (0·088 g.), which on crystallisation from alcohol had m. p. 162—163° alone or mixed with 1,2,8-trimethylphenanthrene picrate. By passing the picrate through a column of alumina (Grade I) and collecting crystalline fractions, 44 mg. of hydrocarbon, m. p. 136—139°, were obtained. Two crystallisations from ethanol followed by sublimation at 140°/10^{-5} mm. gave plates, m. p. and mixed m. p. 145—146°. The two specimens had $\lambda_{max.}$ (in ethanol) 211, 224, 262, 282, 293, 307, 339 mμ (log ε 4·60, 4·39, 4·80, 4·13, 4·13, 4·23, 2·63).

2,9-*Dioxocassenic Acid* (II; R = O, R′ = H).—Cassaic acid (30 mg.) was oxidised as described by Ruzicka, Dalma, and Scott,[10] to yield 21 mg. of diketo-acid, m. p. 246—248°, $[\alpha]_D^{21}$ −159° (in ethanol, *c* 0·8) (Ruzicka *et al.*,[10] m. p. 249°, $[\alpha]_D^{20}$ −152°), $\nu_{max.}$ (KBr disc) 1700 (C=O) and 1647 cm.$^{-1}$ (double bond α to carbonyl group) (Found: C, 72·3; H, 8·6. Calc. for $C_{20}H_{28}O_4$: C, 72·3; H, 8·4%). This compound gave a purple colour with the Zimmermann reagent.

9-*Oxocassenic Acid* (II; R = R′ = H).—2,9-Dioxocassenic acid (500 mg.) in acetic acid (40 ml.) was refluxed with amalgamated zinc (6 g.) concentrated hydrochloric acid (12 ml.) and water (8 ml.) for 8 hr. After working up in the usual manner an acidic solid was obtained (410 mg.; m. p. 180—185°). This was chromatographed in benzene–ether (1 : 2) on M.F.C. silica gel (20 g.) (24 × 1 cm.). The chromatogram was developed with benzene–ether (1 : 2) (200 ml.). Crystalline fractions (400 mg.) were obtained with benzene–ether (1 : 4) and, recrystallised from ether–light petroleum, had m. p. 188—189·5°. 9-*Oxocassenic acid* gave a precipitate with 2,4-dinitrophenylhydrazine, but failed to react in the Zimmermann test;

it had $[\alpha]_D^{20}$ −70° (in ethanol, *c* 0·6), $\lambda_{max.}$ (in ethanol) 220 mμ (log ε 4·2), $\nu_{max.}$ (in chloroform) 1710 (C=O) and 1650 cm.$^{-1}$ (C=C) (Found: C, 75·1; H, 9·8. $C_{20}H_{30}O_3$ requires C, 75·5; H, 9·5%).

Perhydro-1,1,8,12-tetramethyl-7,9-dioxophenanthrene (III; R = H, R′ = R″ = O).—9-Oxocassenic acid (370 mg.) in dry chloroform (90 ml.) was ozonised at −20° to −30° for 65 min., then left to warm to room temperature for 3 hr. Solvent was removed. The resulting ozonide in glacial acetic acid (20 ml.) was decomposed by shaking for 3 hr. with powdered zinc (3 g.) in water (20 ml.), a neutral gum (230 mg.) being obtained. This could not be satisfactorily purified and after subliming twice at 110/10^{-5} mm. was used in the next stage. This gum gave a purple colour with the Zimmermann reagent.

The crude diketone (210 mg.) in dry ether (80 ml.) was treated with ethereal methyl-lithium (from lithium, 1 g., and methyl iodide, 12 g.). The resulting gummy alcohol was heated with selenium (230 mg.) at 340° for 48 hr., then extracted with ether. The extract was washed with sodium hydroxide solution, and afforded a neutral gum (44 mg.). After filtering in ether through alumina this was twice sublimed at 110°/10^{-5} mm., then crystallised twice from methanol, to yield plates (2 mg.), m. p. 108—110° alone or mixed with 1,7,8,9-tetramethylphenanthrene. The alcoholic mother-liquors from crystallisations were converted into the trinitrobenzene derivative, m. p. and mixed m. p. 157—159°, of 1,7,8,9-tetramethylphenanthrene. The ultraviolet absorption of the two specimens were identical [$\lambda_{max.}$ (in ethanol) 217·5, 230, 265, 286, 299, 311, 342, 359 mμ (log ε 4·57, 4·49, 4·75, 4·08, 4·06, 4·08, 2·92, 2·82)].

2-Hydroxyallocassenic Acid.—Cassaic acid (200 mg.) was reduced by the Wolff–Kishner method as modified by Barton, Ives, and Thomas.[11] There was thus obtained the above *compound*, m. p. 224—226° (from methanol), $[\alpha]_D^{20}$ −88° (in ethanol, *c* 1·0) (no absorption above 210 mμ), $\nu_{max.}$ (in Nujol mull) 3490 (OH) and 1708 cm.$^{-1}$ (C=O) (Found: C, 75·0; H, 10·2. $C_{20}H_{32}O_3$ requires C, 75·1; H, 10·0%). It gave no colour with the Zimmermann reagent.

When oxidised with chromic anhydride in the usual manner *2-oxoallocassenic acid* was formed, crystallising from aqueous acetone in needles, m. p. 153—155°, $[\alpha]_D^{20}$ −92° (in ethanol, *c* 0·37), $\nu_{max.}$ (KBr disc) 1733 (CO_2H) and 1703 cm.$^{-1}$ (C=O) (Found: C, 74·9; H, 9·85. $C_{20}H_{30}O_3$ requires C, 75·5; H, 9·5%). The compound showed no absorption characteristic of an αβ-unsaturated carboxylic acid in the 210—230 mμ region and gave a purple colour with the Zimmermann reagent.

Cassaidic Acid.—Sodium borohydride (100 mg.) in water (5 ml.) containing 1 drop of 2N-sodium hydroxide was added dropwise at 35° to cassaic acid (200 mg.) in methanol (40 ml.). After 1 hr. solvent was removed and the residue cooled to 0°, then acidified with dilute hydrochloric acid. The resulting precipitate (178 mg.), recrystallised from ethyl acetate, had m. p. 275° (decomp.), $[\alpha]_D^{20}$ −102° (in ethanol, *c* 1·0) (lit., m. p. 275—277°), $[\alpha]_D^{20}$ −100°), $\nu_{max.}$ (in Nujol mull) 3500 (OH), 1692 (CO_2H), 1645 cm.$^{-1}$ (C=C). This acid formed a *p-phenylphenacyl ester*, plates (from ether–light petroleum), m. p. 113—116°, $[\alpha]_D^{22}$ −97·7° (in chloroform, *c* 1·0) (Found: C, 77·1; H, 7·7. $C_{34}H_{40}O_5$ requires C, 77·0; H, 8·0%). Cassaidic acid gave no colour with the Zimmermann reagent. Engel [12] showed that if dioxocassenic acid is treated with one mol. proportion of sodium borohydride only the 2-ketone group is reduced and cassaic acid is formed.

Ozonolysis of Methyl Cassaidate.—Methyl cassaidate (12 mg.) was ozonised in dry chloroform (12 ml.), yielding a substance which, crystallised from carbon tetrachloride, had m. p. 133—136°, $[\alpha]_D^{20}$ −58° (in chloroform, *c* 0·3), $\nu_{max.}$ 3500 (OH) and 1710 cm.$^{-1}$ (C=O). The compound gave a purple colour with the Zimmermann reagent.

We thank Dr. J. E. Page of Glaxo Laboratories Ltd. for determining the infrared spectrum of several compounds (on a Perkin–Elmer model 21 spectrophotometer), also the Department of Scientific and Industrial Research for a special research grant towards the purchase of an " Infracord " spectrophotometer. We are grateful to Dr. J. F. McGhie for a specimen of 1,2,8-trimethylphenanthrene and its picrate.

School of Pharmacy, Brunswick Square,
London, W.C.1.

[*Received, May 28th,* 1959.]

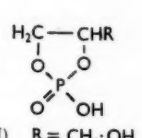
[11] Barton, Ives, and Thomas, *J.*, 1955, 2056.
[12] Engel, *Helv. Chim. Acta*, 1959, **42**, 1127.

726. *The Hydrolysis of* D-*Carboxyethylene Phosphate* (D-*Glyceric Acid 2,3-Cyclic Phosphate*).

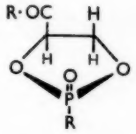
By R. F. Webb and A. J. Duke.

Acid-catalysed hydrolysis of D-carboxyethylene phosphate (D-glyceric acid 2,3-cyclic phosphate) gives the two glyceric acid phosphomonoesters in a different ratio from that in which they are obtained on acid-catalysed equilibration of either of them. Basic hydrolysis is not accompanied by appreciable elimination to give phosphoenolpyruvate.

Ukita *et al.*[1] recently showed that the initial product ratio from the acidic hydrolysis of glycerol 1,2-cyclic phosphate (I) is subject to kinetic control, subsequent slower equilibration of the isomeric glycerol phosphates produced leading to thermodynamic equilibrium between them.[2] We therefore record a further example of such behaviour.[3]



(I) R = $CH_2 \cdot OH$
(II) R = CO_2H



(III) R = O^- or OMe

Ammonium D-3-phosphoglycerate was converted into the 2,3-cyclic phosphate of glyceric acid (D-carboxyethylene phosphate) (II) by treatment with trifluoroacetic anhydride[4] and isolated as the trihydrate of the calcium salt. In N-hydrochloric acid at 100°, this ester was completely hydrolysed to a mixture of the isomeric α- and β-phosphoglyceric acids in about 30 seconds, as judged by paper chromatography.[5] Opening of the ring was complete in 0·023N-acid at 100° in about five minutes. In both cases, the hydrolysis and the subsequent acid-catalysed interconversion of the monoesters were followed polarimetrically, selective enhancement of the rotation of the 3-isomer in neutral 12·5% ammonium molybdate solution permitting determination of the isomer ratio in the product.[6] The final equilibrium value for the rotation obtained in N-acid is in good agreement with that found on equilibration of β-phosphoglyceric acid.[6] That the approach to equilibrium by acid-catalysed phosphate migration is much slower than hydrolysis of the cyclic phosphate in N-acid, and that migration is in fact almost negligibly slow at the lower acidity (the isomer ratio remaining almost unchanged at the value initially produced by hydrolysis of the cyclic phosphate), are evident from the variation of the optical rotation with time (Fig. 1). This is demonstrated even more clearly in Fig. 2, where $\log_{10}(\alpha - \alpha_e)$ is plotted against time,[7] α being a measure of the mole fraction of total phosphoglycerate present as the α-isomer, and α_e its value at migration equilibrium. These plots give values of the extrapolated initial isomer ratio (α- : β-phosphoglycerate) of 1·03 ± 0·07 and, 1·24 ± 0·07, respectively, 51% and 55% of α-isomer, as against 81% at migration equilibrium. Hydrolysis in N-acid at room temperature, in which conditions migration is negligibly slow,[6] also gave a product ratio of 1·20, *i.e.*, 54% of α-phosphoglycerate.

The surprising similarity of the percentages of primary and secondary ester found in this work to those found by Ukita *et al.*[1] for the glycerol phosphates (initially 48% of α-isomer, at equilibrium 81%) is probably fortuitous.

[1] Ukita, Nagasawa, and Irie, *Pharm. Bull.* (*Japan*), 1957, **5**, 127.
[2] Cf. Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 670 *et seq.*
[3] A. J. Duke, Ph.D. Thesis, Cambridge, 1957.
[4] Brown, Magrath, and Todd, *J.*, 1952, 2708.
[5] (*a*) Bandurski and Axelrod, *J. Biol. Chem.*, 1951, **193**, 405; (*b*) Cowgill, *Biochim. Biophys. Acta*, 1955, **16**, 614.
[6] Ballou and Fischer, *J. Amer. Chem. Soc.*, 1954, **76**, 3188.
[7] Glasstone, "Textbook of Physical Chemistry," van Nostrand, New York, 1946, pp. 1052—1053.

Hence, it appears that in the interconversion of isomeric 2-hydroxyalkyl phosphates under acidic conditions, the isomer ratio at equilibrium is determined by the relative rates of closure of the isomers to give a cyclic transition state or intermediate, rather than by any tendency of the related cyclic phosphodiester to open at the secondary rather than the primary position.

One of the original purposes of the preparation of D-carboxyethylene phosphate was the hope that its reaction with alkali might afford a convenient preparative method for phosphoenolpyruvate, by the known elimination reaction of β-acyloxy-acids (and their esters).[8] However, treatment of the cyclic ester in various alkaline conditions gave no trace of phosphoenolpyruvate on paper chromatography of the hydrolysates, and comparison of the ultraviolet absorption of the products in the 210—220 mμ region with that of authentic phosphoenolpyruvate and pyruvic acid indicated that less than 0·5% of elimination occurred in the total course of the reaction. Also, the product of methylation of the cyclic ester with diazomethane opened to give a solution showing negligible ultraviolet

FIGS. 1 and 2. *Change of rotation in molybdate solution on hydrolysis of* D-*carboxyethylene phosphate by* (*A*) N-*acid and* (*B*) 0·023N-*acid.*

FIG. 1.

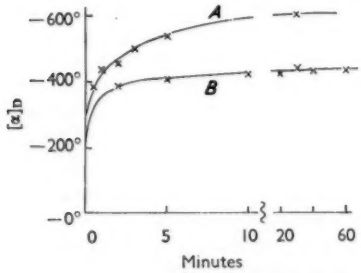
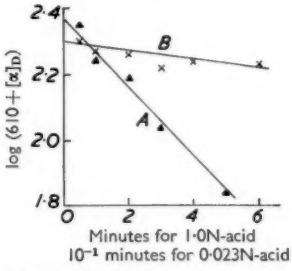


FIG. 2.



$[\alpha]_D$ *of* α-*phosphoglyceric acid* [6] = −740°.
In Fig. 2, *intercepts at* $t = 0$ *are* 2·37 ± 0·03 *for* (*A*) *and* 2·30 ± 0·02 *for* (*B*).

absorption when compared with a solution of similarly methylated phosphoenolpyruvic acid. Absence of elimination in these cases is presumably due to the inability of the four atoms involved (see III) to adopt the planar configuration generally considered necessary for easy base-catalysed elimination.[9]

EXPERIMENTAL

Calcium D-*Carboxyethylene Phosphate* (D-*glyceric acid calcium* 2,3-*phosphate*).—Barium α-D-phosphoglycerate (dihydrate, 5·00 g.) was shaken with ammonium sulphate (1·85 g., one equiv.) in water (50 ml.) for 48 hr. The solution was filtered and evaporated, and the residue dried for 2 hr. at 50—60°/1 mm., then for 4 days over P_2O_5 at 10^{-4} mm. and room temperature, giving anhydrous ammonium α-D-phosphoglycerate, (2·96 g., 96%). This was dissolved with shaking in freshly distilled trifluoroacetic anhydride (50 ml.) and set aside at room temperature overnight. Dry toluene (25 ml.) was then added, and the solution evaporated *in vacuo via* a tube packed with silica gel, a P_2O_5 guard tube being used on the air-leak. The residue was finally heated at 40°, first at 15 mm., then at 0·5 mm. for 2 hr., dissolved in sodium-dried dioxan (15 ml.), and poured into a stirred slurry of lithium carbonate (5·0 g.) previously saturated with carbon dioxide. After 5 minutes' stirring, the solution (pH 8—9) was filtered, evaporated at ≤40° to about 30 ml., and diluted *slowly* with four volumes of ethanol. The precipitate was filtered off and rejected, and the filtrate was evaporated to dryness, again at ≤40°. The residue from this evaporation was dissolved in 10% aqueous lithium chloride (25 ml.), and the solution diluted slowly with ethanol (100 ml.) and filtered. The two precipitates from 80% ethanol

[8] Linstead, Owen, and Webb, *J.*, 1953, 1211, 1218, 1225.
[9] Barton, *J.*, 1953, 1027, and references there cited.

contained all the phosphorus-containing contaminants running more slowly than the desired product on paper chromatograms.[5]

The solution was again evaporated at $<40°$, and the residue dissolved in water (50 ml.) containing calcium chloride hexahydrate (3·0 g.). This solution was evaporated under reduced pressure to 20 ml., then filtered, and the product precipitated by addition of ethanol (10 volumes) with stirring during 20 hr. and filtered off. As this product contained traces of lithium and chloride ions, it was reprecipitated twice under similar conditions, first from water (8 ml.) containing calcium chloride (150 mg.) on addition of ethanol (80 ml.), then similarly without the addition of calcium chloride. Finally the product was washed with ethanol (15 ml.) and dry ether (30 ml.), giving *calcium* D-*carboxyethylene phosphate trihydrate* (794 mg., 22·7%) which was homogeneous on paper chromatograms,[5] was free from chloride and lithium ions, and had $[\alpha]_D^{20}$ +49° (*c* 1·1 in water), $[\alpha]_D^{20}$ −43° (*c* 0·6 in 12·5% ammonium molybdate solution) (Found: C, 13·6; H, 3·4; P, 12·3; ash 52·7. $C_3H_3O_6PCa,3H_2O$ requires C, 13·8; H, 3·5; P, 11·9; ash 52·4%).

Loss of weight on drying could not be determined, as the compound showed appreciable hydrolysis by its own water of crystallisation at the temperatures required for any significant loss of weight (50—60°).

Acidic Hydrolyses.—(i) *In conditions causing phosphate migration*: N-*acid*. Weighed samples of calcium D-carboxyethylene phosphate (~5 mg.) were heated in tubes at 100°, and preheated N-hydrochloric acid (0·25 ml.) was then added. After the required time, N-sodium hydroxide (0·25 ml.) was added, and the samples were cooled and made to 1·00 ml. with 25% ammonium molybdate solution, and the rotations of the resulting solutions were determined:

Time (min.)	½	1	2	3	5	30
$[\alpha]_D$	−385°	−435°	−455°	−500°	−540°	−610°
$\log_{10}\{610 + [\alpha]_D\}$	2·35	2·24	2·19	2·04	1·84	—

Hydrolysis by N-hydrochloric acid at room temperature gave a value of $[\alpha]_D$ −405° at 30 and 60 min.

Samples were treated in water with one equivalent of ammonium carbonate and then centrifuged, the residues were washed at the centrifuge, and the combined supernatant liquids were heated with half their volume of 3N-hydrochloric acid and analysed as above. The same results were obtained, within experimental error, as in determinations on the calcium salt, indicating the absence of a calcium ion effect on isomer ratio at this acidity.

(ii) *In conditions where migration is negligibly slow*: 0·023N-*acid*. Calcium D-carboxyethylene phosphate (61·0 mg.) in water (5 ml.) was passed down a column of Amberlite IR-120 (H^+ form), and the eluate made up to 10 ml. Aliquot parts (0·5 ml.) were heated in sealed tubes at 100°, and at intervals tubes were cooled and opened, and the contents basified with ammonia. Preliminary experiments with α-phosphoglycerate had shown that exact neutralisation was not critical for its determination by rotation in molybdate solutions, provided that a weak base was used. The samples were made to 1·00 ml. with 25% ammonium molbydate solution, and the rotations determined as before:

Time (min.)	2	5	10	20	30	40	60
$[\alpha]_D$	−385°	−410°	−425°	−430°	−445°	−435°	−440°
$\log_{10}\{610 + [\alpha]_D\}$	2·35	2·30	2·27	2·26	2·22	2·24	2·23

A specific calcium ion effect on the initial isomer ratio was observed in the range pH 1·5—2.

In both the above hydrolyses, the cyclic ester was no longer present on paper chromatograms [5a] after the shortest hydrolysis time, the product consisting of the two isomeric phosphoglycerates, separated in the system ethanol–formic acid–water on ammonium molybdate-treated paper.[5b]

The authors thank Sir Alexander Todd for his interest and encouragement, and the Department of Scientific and Industrial Research for a maintenance award (to A. J. D.).

UNIVERSITY CHEMICAL LABORATORY,
LENSFIELD ROAD, CAMBRIDGE.

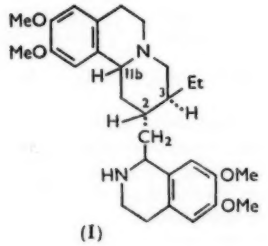
[*Received, June 2nd*, 1959.]

727. *Chemical Constitution and Amœbicidal Action. Part V.* Stereochemistry of Emetine.*

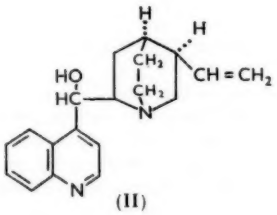
By A. Brossi, A. Cohen, J. M. Osbond, P. Plattner, O. Schnider, and J. C. Wickens.

An investigation of the stereochemistry of emetine has led to formula (I). The 2- and the 3-substituent are in a *trans*-relation and the 11b-hydrogen atom is *cis* to the 2-hydrogen atom.

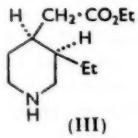
Recent preliminary communications [1-6] have described the relative configurations at the four asymmetric centres (2, 3, 11*b*, and 1′) of emetine. The synthesis of emetine and three stereoisomers described in Part IV * forms the basis of the present investigation. These compounds were derived from the two acetic acids (VI; A and B). The former led to (±)-emetine and (±)-isoemetine; therefore determination of the configuration of one of these acids would reveal that of emetine at $C_{(2)}$ and $C_{(3)}$. The possible biogenetic link between the cinchona and ipecacuanha alkaloids [7] led us to degrade cinchonine (II) by known methods [8,9] to ethyl cincholoiponate (III), which is known [8] to have *cis*-substituents at positions 3 and 4, in order to link the latter compound with one of the acids (VI).



(I)



(II)



(III)

Condensing the ester (III) with 3,4-dimethoxyphenethyl iodide gave the *cis*-4-piperidylacetate (IV) which was reduced with lithium aluminium hydride to the *cis*-(+)-alcohol (V), m. p. 49·5—51°, $[\alpha]_D$ +9°. Esters of the synthetic acids (VI; A and B) were reduced similarly to the (±)-alcohols (V; A), m. p. 64·5—65·5°, and (B), m. p. 76·5—79·5°. The (±)-alcohol (V; A) was characterised by a crystalline hydrobromide and hydrogen oxalate; the same salts of the (±)-alcohol (V; B) and *cis*-(+)-alcohol (V), however, did not crystallise. Infrared spectroscopy of the three bases in solution showed that the *cis*-(+)-alcohol V (from cinchonine) and (±)-alcohol (V; B) were identical whereas the spectrum of the alcohol (V; A) showed several differences. Emetine, which we had located in the A series (Part IV), therefore has the *trans*-configuration at $C_{(2)}$ and $C_{(3)}$, in

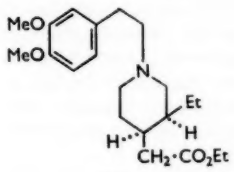
* Part IV, *J.*, 1959, 3530.

[1] Battersby, Binks, Davidson, Davidson, and Edwards, *Chem. and Ind.*, 1957, 982; Battersby and Garratt, *Proc. Chem. Soc.*, 1959, 86.
[2] Battersby and Cox, *Chem. and Ind.*, 1957, 983.
[3] (*a*) van Tamelen, Aldrich, and Hester, *J. Amer. Chem. Soc.*, 1957, **79**, 4817; (*b*) van Tamelen and Hester, *ibid.*, 1959, **81**, 507.
[4] (*a*) Brossi, Cohen, Osbond, Plattner, Schnider, and Wickens, *Chem. and Ind.*, 1958, 491; (*b*) Osbond, *ibid.*, 1959, 257.
[5] Battersby, *ibid.*, 1958, 1324.
[6] Battersby and Turner, *ibid.*, p. 1324.
[7] Turner and Woodward in "The Alkaloids," Manske and Holmes, 1953, **3**, 54.
[8] Prelog and Zalan, *Helv. Chim. Acta*, 1944, **27**, 535.
[9] Kaufmann, Rothlin, and Brunnschweiler, *Ber.*, 1916, **49**, 2299.

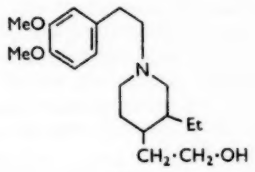
XUM

agreement with conclusions by Battersby and Cox [2] and van Tamelen, Aldrich, and Hester.[3]

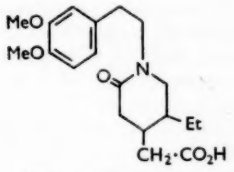
The 11b-hydrogen atom has been given the configuration shown in (I) by Battersby *et al.*[1] and van Tamelen *et al.*,[3] and later Battersby [5] advanced further evidence and arguments supported by a synthesis of emetine [6] which would be expected to give an axial attachment of the 11b-hydrogen atom. At first our results were not in agreement with this conclusion [4a] but after Battersby's further preliminary communications [5,6] our evidence was re-examined and a correction was made.[4b]



(IV)



(V)



(VI) A, m.p. 154–156°
B, m.p. 152–153°

Battersby *et al.*[1] have also determined the absolute configuration at position 1', and van Tamelen and Hester [3b] have determined the relative configuration. We observed [4a] that the rate of dehydrogenation, by mercuric acetate,[10] of isoemetine (Ab_2) to the rubremetinium ion is *ca.* twice as fast as that of emetine (the 1'-epimer).

Experimental

Ethyl Cincholoiponate (III).—This ester was prepared from cinchonine by the method of Kaufmann, Rothlin, and Brunnschweiler.[9] Hydrolysis of the benzoylcincholoiponitrile with barium hydroxide gave a mixture of the corresponding free amino-nitrile and -acid and unchanged benzoyl-nitrile. However, hydrolysis with concentrated hydrochloric acid for 7 hr. gave cincholoiponic acid which without isolation was esterified with ethanol saturated with hydrogen chloride. Ethyl cincholoiponate, b. p. 134—138°/14 mm., n_D^{20} 1·4680 was obtained, in 70% yield (for the two steps) (Prelog and Zalan [8] give b. p. 137—138°/11 mm., n_D^{20} 1·4675). The hydrochloride, after crystallisation from acetone, had m. p. 160—161·5°, $[\alpha]_D^{21}$ −11·07° (*c* 2·981 in EtOH) [lit.,[8] m. p. 159—160°, $[\alpha]_D^{23}$ −9·3° ± 1° (*c* 2·576 in EtOH)].

cis-1-(3,4-*Dimethoxyphenethyl*)-4-*ethoxycarbonylmethyl*-3-*ethylpiperidine Hydrochloride* (cf. IV).—Ethyl cincholoiponate (3·99 g.), 3,4-dimethoxyphenethyl iodide (5·84 g.), and anhydrous potassium carbonate (5·0 g.) were refluxed in dry benzene (50 c.c.) for 3·5 hr. After addition of water, the benzene extracts were washed with 2N-hydrochloric acid (3 × 25 c.c.). The base liberated from the acid extracts was extracted with ether (3 × 25 c.c.) and dried (Na_2SO_4). Treatment of the resulting basic oil (5·8 g.) in ether with hydrogen chloride gave the *hydrochloride* which crystallised from acetone or methanol–ether as needles, m. p. 126—129° (3·30 g., 41%) (Found: C, 62·1; H, 8·7; N, 3·4; Cl, 8·7. $C_{21}H_{33}O_4N,HCl,0{\cdot}5H_2O$ requires C, 61·7; H, 8·6; N, 3·4; Cl, 8·7%). The infrared spectrum confirmed the structure and showed a hydroxyl band due to hydration of the salt. The neutral benzene extract gave unchanged iodide (2·39 g.) on evaporation.

cis-(+)-1-(3,4-*Dimethoxyphenethyl*)-4-2'-*hydroxyethyl*-3-*ethylpiperidine* (V).—The free base from the above ester hydrochloride (3·99 g.) was added in ether (20 c.c.) to a solution of lithium aluminium hydride (0·38 g.) in ether (10 c.c.) during 0·25 hr. with stirring. After refluxing for 2·5 hr., the solution was cooled and treated with ethyl acetate (1 c.c.), water, and dilute acid. The acid layer was extracted once with ether, made alkaline with 2N-sodium hydroxide, extracted with ether (3 × 30 c.c.), and dried (Na_2SO_4). Removal of the ether gave the basic alcohol (3·24 g.) which, however, did not give a crystalline hydrobromide even when seeded

[10] Battersby and Openshaw, *J.*, 1949, S67.

XUM

with the hydrobromide of the (±)-alcohol (V; A) (see below). When the base was seeded with the (±)-base (V; B) (see below) it immediately crystallised. Crystallisation from light petroleum (b. p. 40—60°) gave the pure *alcohol*, m. p. 49·5—51°, $[\alpha]_D^{22}$ +9·0° ±1·26° (*c* 2·399 in EtOH) (Found: C, 71·6; H, 9·8; N, 4·4. $C_{19}H_{31}O_3N$ requires C, 71·0; H, 9·7; N, 4·4%).

The acid (VI; A), m. p. 154—156°, was converted into the ethyl ester which (4·0 g.) was added in dry tetrahydrofuran (20 c.c.) to lithium aluminium hydride (1·2 g.) in dry tetrahydrofuran (50 c.c.) during 0·25 hr. The solution was then refluxed for 4 hr., cooled, and decomposed with ethyl acetate, water, 2N-sulphuric acid, and ether. The ether layer was extracted twice with sulphuric acid, the acid extracts were combined and made alkaline with 25% potassium hydroxide solution, and the basic alcohol was extracted with ether and dried (Na_2SO_4). The ether was removed and the *hydrobromide* was prepared; this crystallised from ethanol–ether as prisms (2·67 g.), m. p. 174—176·5° (Found: C, 57·0; H, 8·0; N, 3·5; Br, 19·45. $C_{19}H_{31}O_3N$,HBr requires C, 56·7; H, 8·0; N, 3·5; Br, 20·1%). The hydrogen oxalate crystallised from ethanol–ether as prisms, m. p. 141—144° (Found: C, 60·4; H, 8·3; N, 3·4. $C_{19}H_{31}O_3N,H_2C_2O_4,0{\cdot}5H_2O$ requires C, 60·0; H, 8·1; N, 3·3%). Conversion of the hydrobromide into the base and crystallisation from light petroleum (b. p. 60—80°) gave the pure (±)-*alcohol* as prisms, m. p. 64·5—65·5° (Found: C, 71·1; H, 9·8; N, 4·5%).

The corresponding acid (VI; B) (2·0 g.), m. p. 152—153°, was similarly converted into the ethyl ester and reduced in tetrahydrofuran (50 c.c.) with lithium aluminium hydride (0·7 g.). After 4 hours' refluxing, the (±)-alcohol (V; B) was obtained as described above, as prisms (1·2 g.), m. p. 76·5—79·5° (Found: C, 71·6; H, 9·8; N, 4·3%). The base failed to give a crystalline hydrobromide, hydrogen oxalate, or hydriodide.

Mixed m. p.s between these bases were unsatisfactory; thus between (±)-A and (±)-B the mixed m. p. was 62·5—68°; between (±)-A and *cis*-(+)-(V), 46—55°; between (±)-B + *cis*-(+)-(V), 48—70°. Paper-chromatographic separation was also attempted. Several solvent systems were used but although each isomer gave only one spot they could not be separated from each other. The infrared spectra of the three bases in carbon disulphide, however, showed that the *cis*-(+)-base and (±)-B-isomer were identical. Comparison of the infrared spectra of the *cis*-(+)-base and (±)-A-isomer showed them to be very similar, but small, significant differences were evident in the 1093—1075, 987, 937—938, and 870 cm.$^{-1}$ regions.

Rate of Formation of Rubremetinium Salt from Emetine and Isoemetine (Stereoisomer, Ab_2).—(+)-Emetine dihydrochloride and synthetic (±)-isoemetine (Ab_2) were dehydrogenated [10] to rubremetinium salts, the rate of reaction being followed kinetically in the following way. The dihydrochloride (0·1000 g.) in water (50 c.c.) at 80—90° was treated with mercuric acetate (0·43 g.) in acetic acid (0·5 c.c.) and water (49·5 c.c.) previously warmed to 60°. The solution was then kept in a boiling-water bath under a reflux condenser. From this solution a portion (5 c.c.) was extracted every 15 min. and diluted to 250 c.c. with distilled water. The ultraviolet absorption was then measured at 434 mμ; the rubremetinium ion has a maximum absorption at this wavelength whereas intermediate dehydrogenated products, such as the dehydro- and tetradehydro-isoquinoline moieties, do not absorb there. After 30 and 180 min. the extinction coefficients (E) for emetine were 0·015 and 0·116, and for isoemetine 0·025 and 0·22; all other results fell on straight lines between these values. The straight-line graph shows that (±)-isoemetine is converted into the rubremetinium salt *ca.* twice as fast as is emetine.

We thank Dr. A. Wagland for the infrared spectra.

Roche Products Limited, Welwyn Garden City, Herts.
F. Hoffmann-La Roche & Co., Basle, Switzerland.

[*Received, April 21st,* 1959.]

XUM

728. *Reactions of Disodium Pentacyanoamminoferrate with Aromatic Amines. Part IV.*[1] *The Preparation and Properties of Compounds containing the μ-p-Phenylenediaminebis(pentacyanoferrate) Ion.*

By E. F. G. Herington.

The reactions of an alkaline solution of disodium pentacyanoamminoferrate with *p*-aminophenol [2,3] and with aniline [2,4] have been investigated and this Note reports results with *p*-phenylenediamine. The reaction of disodium pentacyanoamminoferrate with *p*-phenylenediamine produced a dark blue solution exhibiting a single absorption band in the range 400—1000 mμ of half-width 150 mμ, with a maximum at 685 mμ. Paper electrophoresis showed that the solution contained mainly one anionic species and that the complex was only slightly decomposed after one week. Continuous-variation experiments with freshly prepared solutions, buffered with borax, indicated that the disodium salt reacted with *p*-phenylenediamine in the molar ratio 2 : 1. On mixing of solutions of *p*-phenylenediamine (0·001 mole in 20 ml.) and disodium pentacyanoamminoferrate (0·002 mole in 20 ml.) adjusted to pH 11·4, the pH fell to 8·4 and 0·0015 equivalent of sodium hydroxide was needed to restore the pH to 11·4. A purified sample of the zinc salt, which exhibited a strong band at 2093 cm.$^{-1}$ resembling in intensity and band-width that found in zinc ferrocyanide,[5] gave the correct analysis for $Zn_3[Fe(CN)_5{\cdot}HN{\cdot}C_6H_4{\cdot}NH{\cdot}Fe(CN)_5],4H_2O$. Reduction of the sodium salt with dithionite regenerated *p*-phenylenediamine.

It is suggested that the reaction can be represented by the equation

$$2Na_3[Fe(CN)_5{\cdot}NH_3] + H_2N{\cdot}C_6H_4{\cdot}NH_2 + 2NaOH = Na_6[Fe(CN)_5{\cdot}HN{\cdot}C_6H_4{\cdot}NH{\cdot}Fe(CN)_5] + 2NH_3 + 2H_2O$$

By the use of a spraying technique [3,4] it was established that the following salts of the complex anion are insoluble in dilute acetic acid; cupric, blue; silver, blue; zinc, violet blue; cadmium, blue; mercurous and mercuric, black; lead, blue; zirconium, blue; hafnium, blue; thorium, green blue; chromium, blue; uranyl, grey; manganese, brown; ferric, blue; cobalt, green; nickel, green; palladium, green.

Experimental.—Experiments were carried out as described earlier,[3,4] except that an ordinary glass electrode was used for the pH measurements.

Zinc μ-p-phenylenediaminebis(pentacyanoferrate). On to *p*-phenylenediamine (0·19 g.) was poured a solution containing disodium pentacyanoamminoferrate monohydrate (0·7 g.) in 0·1N-sodium hydroxide (5 ml.). The mixture was shaken for 30 min., then portions (2·5 ml.) were put on the upper ends of two Whatman's seed test papers. The papers were inserted into a preparative paper-electrophoresis apparatus,[4] current was passed, the resulting dark blue bands were cut out, and the material extracted from them with 0·1N-sodium hydroxide at room temperature. Zinc nitrate (3 ml.; M) was added to the resulting solution, and then glacial acetic acid (12 ml.). The blue precipitate was removed by centrifugation, and the gel was washed with water until the decanted liquid was neutral. The *zinc salt* was dried [NaOH, then $Mg(ClO_4)_2$ in a vacuum] [Found: C, 26·1; H, 1·9; N, 21·2; Zn, 26·0; Fe, 15·0. $Zn_3[Fe(CN)_5{\cdot}HN{\cdot}C_6H_4{\cdot}NH{\cdot}Fe(CN)_5],4H_2O$ requires C, 25·7; H, 1·9; N, 22·4; Zn, 26·3; Fe, 15·0%].

This note is published by permission of the Director, National Chemical Laboratory.

National Chemical Laboratory,
Teddington, Middlesex.

[*Received, December 10th*, 1958.]

[1] Part III, Herington, *J.*, 1958, 4771.
[2] Herington, *Nature*, 1955, **176**, 80.
[3] Herington, *J.*, 1956, 2747.
[4] Herington, *J.*, 1958, 4683.
[5] Herington and Kynaston, *J.*, 1955, 3555.

XUM

729. *Preparation of* 1-*Benzylpiperazine.*

By J. Cymerman Craig.

For the preparation of 1-monosubstituted, and thence of 1,4-unsymmetrically disubstituted piperazines it is usual to protect one of the nitrogen atoms by use of the 1-ethoxycarbonyl derivative.[1] The use of 1-benzylpiperazine hitherto required either fractional distillation,[2] often after long reaction, or 1-ethoxycarbonylpiperazine as intermediate.[3] We found[4] that 1 mol. each of hydrogen chloride and benzyl chloride gave a precipitate of piperazine dihydrochloride and a solution from which 1-benzylpiperazine could be obtained. A convenient preparation of 1-benzylpiperazine is now described, from 1 mol. each of piperazine, piperazine dihydrochloride, and benzyl chloride; 98% of the piperazine dihydrochloride is recovered, and the solution affords 4-benzylpiperazinium chloride in 93% yield.

The formulation of 4-benzylpiperazinium chloride is supported by its infrared spectrum (paraffin mull), which shows no absorption in the –NH region but bands at 2920 and 2810 cm.$^{-1}$ (NH_2^+ stretching) and 1600 cm.$^{-1}$ (NH_2^+ deformation).[5]

When kept in air or treated with carbon dioxide, 1-benzylpiperazine formed crystals which decomposed when heated or on attempted recrystallisation, regenerating the base. They liberated carbon dioxide in cold mineral acid, and gave analytical figures corresponding to 4-benzylpiperazinium carbonate $(Ph{\cdot}CH_2{\cdot}N<[CH_2{\cdot}CH_2]_2>NH_2^+)_2CO_3^{2-}$. However, their infrared spectrum (paraffin mull) was devoid of absorption at 878 or 1440 cm.$^{-1}$ (ionic carbonates[6,7]) but included OH absorption and a band at 1662 cm.$^{-1}$ given by hydrated inorganic salts[6,8] and presumably corresponding to the band at 1646 cm.$^{-1}$ shown[9] by liquid water at 20°. *E.g.*, sodium carbonate decahydrate (paraffin mull) had, in addition to the bands at 700 (w), 879 (s), and 1445 (s) cm.$^{-1}$, strong absorption at 1655 and 3220—3375 cm.$^{-1}$ which was absent in the anhydrous salt. The substance formed from 1-benzylpiperazine must therefore be 4-benzylpiperazinium 4-benzylpiperazine-1-carboxylate monohydrate (I), and this was confirmed by determination of the equivalent weight.

$$Ph{\cdot}CH_2{\cdot}N<[CH_2{\cdot}CH_2]_2>NH_2^+ \quad Ph{\cdot}CH_2{\cdot}N<[CH_2{\cdot}CH_2]_2>N{\cdot}CO_2^-,H_2O \quad (I)$$

In its behaviour towards carbon dioxide, 1-benzylpiperazine thus resembles *N*-ethoxycarbonylethylenediamine[1] but differs from piperazine which forms the betaine $^+H_2N<[CH_2{\cdot}CH_2]_2>N{\cdot}CO_2^-$.[10]

For determination[5] of their infrared spectra, 1-methylpiperidinium and 1-ethylmorpholinium iodide and tetrahydro-1,4-thiazine hydriodide were prepared.

Experimental.—*1-Benzylpiperazine.* To a solution of piperazine dihydrochloride monohydrate (22·1 g., 0·125 mole) and piperazine hexahydrate (24·3 g., 0·125 mole) in absolute ethanol (50 c.c.) at 65° benzyl chloride (15·8 g., 0·125 mole) was added in 5 min. with stirring. After a further 25 minutes' stirring at 65°, the solution was cooled, kept at 0° for 30 min., and filtered. The solid was washed with ice-cold absolute ethanol and dried at 70°, giving recovered piperazine dihydrochloride (21·8 g., 98%) as needles, m. p. 310° (decomp.). Addition of 10N-absolute-alcoholic hydrogen chloride (25 c.c., 0·25 mole) at 0° to the combined filtrate and washings

[1] Moore, Boyle, and Thorn, *J.*, 1929, 39.
[2] Baltzly, Buck, Lorz, and Schon, *J. Amer. Chem. Soc.*, 1944, **66**, 263; Buck and Baltzly, U.S.P. 2,415,785, 2,415,786, 2,415,787; Wellcome Foundation, B.P. 578,342; Lutz and Shearer, *J. Org. Chem.* 1947, **12**, 771.
[3] Horrom, Freifelder, and Stone, *J. Amer. Chem. Soc.*, 1955, **77**, 753.
[4] Cymerman Craig, Rogers, and Tate, *Austral. J. Chem.*, 1956, **9**, 397.
[5] Stone, Craig, and Thompson, *J.*, 1958, 52; Heacock and Marion, *Canad. J. Chem.*, 1956, **34**, 1782.
[6] Miller and Wilkins, *Analyt. Chem.*, 1952, **24**, 1253.
[7] Underwood, Toribara, and Neuman, *J. Amer. Chem. Soc.*, 1955, **77**, 317; Gatehouse, Livingstone, and Nyholm, *J.*, 1958, 3137.
[8] Corbridge and Lowe, *J.*, 1954, 493.
[9] Fox and Martin, *Proc. Roy. Soc.*, 1940, *A*, **174**, 234.
[10] Majert and Schmidt, *Ber.*, 1890, **23**, 3718; Rosdalksy, *J. prakt. Chem.*, 1896, **53**, 19.

XUM

precipitated plates which were washed (with benzene) and dried at 70°, giving 1-benzylpiperazine dihydrochloride (29·0 g., 93%), m. p. 253—254° (sintering), then 279—280° (decomp.). Baltzly, Buck, Lorz, and Schon [2] give m. p. 253°.

A solution of this solid (29·0 g.) in water (50 c.c.) was basified to pH >12 with 5N-sodium hydroxide and extracted with chloroform, giving 1-benzylpiperazine (20 g., 91%), n_D^{25} 1·5468. With benzoyl chloride this gave 1-benzoyl-4-benzylpiperazine hydrochloride (91·5%), m. p. 245—245·5°. Baltzly, Buck, Lorz, and Schon [2] report m. p. 245°. Distillation of the base afforded pure 1-benzylpiperazine, b. p. 76—80°/1 mm., n_D^{16} 1·5485, n_D^{25} 1·5440 (lit.,[3] b. p. 89—96°/0·2 mm., n_D^{28} 1·5430).

4-Benzylpiperazinium chloride. (*a*) The filtrate from the recovered piperazine dihydrochloride obtained in the preparation of 1-benzylpiperazine described above gave, on removal of the solvent *in vacuo*, *4-benzylpiperazinium chloride*, plates (from absolute ethanol), m. p. 167—168° (Found: C, 61·65; H, 7·95; N, 12·75. $C_{11}H_{16}N_2$,HCl requires C, 62·1; H, 8·0; N, 13·15%). Treatment with ethanolic hydrogen chloride gave 1-benzylpiperazine dihydrochloride (m. p. and mixed m. p.). (*b*) 1-Benzylpiperazine in ether with ethanolic hydrogen chloride (1 mol.) afforded the same salt, m. p. and mixed m. p. 167·5—168°.

Reaction of 1-benzylpiperazine with carbon dioxide. (*a*) 1-Benzylpiperazine was rapidly transformed in air into *4-benzylpiperazinium 4-benzylpiperazine-1-carboxylate*, m. p. 99—100° (decomp.; rapid heating) [Found: C, 66·9, 66·6; H, 8·3, 8·2%; equiv. (potentiometric titration with 0·2N-NaOH in 33% alcohol), 404. $C_{23}H_{32}O_2N_4,H_2O$ requires C, 66·65; H, 8·25%; equiv., 414]. The water of crystallisation was not removed by prolonged drying *in vacuo*. Infrared absorption maxima (paraffin mull) were at 3390 (s, asymm. OH stretching), sh 3270 (m, symm. associated OH stretching), 2920 and 2850 (s, NH_2^+ stretching), 1662 (m, OH deformation), 1616 (m, NH_2^+ deformation), 1526 and 1420 (s, CO_2^-), and 1000 cm.$^{-1}$ (s, OH deformation). In cold alcoholic hydrogen chloride it gave quantitatively 1-benzylpiperazine dihydrochloride (m. p. and mixed m. p.). (*b*) Ethereal 1-benzylpiperazine with carbon dioxide at room temperature gave the same product, m. p. and mixed m. p. 99—100° (decomp.) (Found: C, 66·65; H, 8·25%).

The following salts were prepared by standard methods: *1-methylpiperidinium*, needles (from ethanol), m. p. 121·5—122° (Found: C, 31·8; H, 6·15. $C_6H_{13}N$,HI requires C, 31·75; H, 6·2%), and *1-ethylmorpholinium iodide*, plates (from ethanol), m. p. 147—148° (Found: N, 5·5. $C_6H_{13}ON$,HI requires N, 5·75%); *tetrahydro-1,4-thiazine hydriodide*, cream plates (from ethanol), m. p. 156—157° (Found: N, 5·95. C_4H_9NS,HI requires N, 6·05%).

The author is indebted to the Nuffield Foundation for a Dominion Travelling Fellowship, and to Professor E. R. H. Jones, F.R.S., for kindly affording laboratory facilities.

Dyson Perrins Laboratory, Oxford.
[Present address: Organic Chemistry Department, The University of Sydney.]

[*Received, December 19th*, 1958.]

---

730. *Isomer Ratios in the Nitration of 6-Acylamino-1,2,3,4-tetrahydronaphthalenes.*

By E. R. Ward and B. D. Pearson.

The present work arose out of attempts to improve the availability of 6-amino-7-nitro-1,2,3,4-tetrahydronaphthalene,[1] an essential intermediate in the synthesis of many 2,3-derivatives of tetralin and naphthalene, but is also of interest in relation to the reactivity of tetralin compounds to electrophilic reagents. Tetralin has the carbon skeleton of naphthalene, but it might be compared superficially to *o*-xylene though the steric situations in the two systems must differ. The Table presents data for the nitration of 6-acylamino-1,2,3,4-tetrahydronaphthalenes.

[1] Ward and Pearson, *J.*, 1959, 1676.

The yield given in the Table represents the yield of *N*-acylated compounds, isolated by chromatography, in relation to the amount of original amide. The probable accuracy of the chromatographic separation is ±1%. The losses experienced with the acetyl derivative are normal in this type of experiment and are largely accounted for by hydrolysis, followed

Acyl	Conditions *	HNO_3 (mol.)	Yield (%)	Products: posn. of substn. & yields (%)
Acetyl	*A*, 50°	1	80	7(42); 5(38)
Acetyl	*A*, 50°	1·5	80	7(43); 5(34); 5,7(3)
Acetyl	*B*, 0°	1	96·5	8(87); 7(8); 5(1·5)
Tosyl	*C*, 35°	1	96	7(40); 5(53); 5,7(3)
Tosyl	*C*, 35°	1·2	94	7(36); 5(28); 5,7(30)

* A, acetic anhydride–nitric acid (*d* 1·42). *B*, Sulphuric acid (*d* 1·84)–nitric acid (*d* 1·42). *C*, Acetic acid–nitric acid (*d* 1·5).

by oxidation and/or diazotisation of the free amine. Experiments in which 6-acetamido-1,2,3,4-tetrahydro-5- and -7-nitronaphthalene were dissolved in the appropriate volume of acetic anhydride containing nitric acid (0·5 mol.) and left overnight showed that whilst the latter could be recovered almost quantitatively there was an 80% loss of the former (*ca.* 10% due to dinitration).

It is probable that for mononitration of both acylated derivatives the 5- is rather more reactive than the 7-position, this being obscured for the acetyl derivative by reason of the much greater losses of the 5- than of the 7-nitro-isomer (see above). It is difficult to account for this since there may be some steric hindrance from the "*peri*"-methylene group at the 5-position and one might expect the 7- to be more activated than the 5-position by electron-supply from the aliphatic ring (cf. Ingold [2]). However, in dinitration of the sulphonamido-compound it is clear that a "*peri*"-steric effect is operating whereby the tautomeric effect of the 5-nitro-group is reduced, so increasing the reactivity of the 5-nitro- relative to that of the 7-nitro-isomer. Under salt-forming conditions (cf. Ward *et al.*[3]) the acetyl compound is, as expected, predominantly substituted at the 8-position. Some reaction appears to occur through the unprotonated form, although the much lower reactivity of the 5- than of the 7-position may be partly accounted for by the much greater solubility of the 5-isomer, with relatively greater losses in isolation.

Schroeter [4] claimed that nitration of 5-acetamido-1,2,3,4-tetrahydronaphthalene in sulphuric acid produced a mixture of 6-, 7-, and 8-nitro-derivatives, the last greatly predominating (although even the yield of this was only *ca.* 45%). We were unable to repeat this work, finding that the yield of 8-nitro-isomer was much lower and that considerable dinitration occurred. However, working in acetic acid–acetic anhydride we obtained the 6-nitro-amide in *ca.* 45% yield. Attempts to carry out a quantitative study of this nitration were frustrated by our inability to separate either the mixed nitro-amides or the corresponding nitro-amines by column chromatography.

Experimental.—*1,2,3,4-Tetrahydro-6-toluene-*p*-sulphonamidonaphthalene.* Obtained in almost quantitative yield by refluxing 6-amino-1,2,3,4-tetrahydronaphthalene with toluene-*p*-sulphonyl chloride in pyridine for 7 hr., this *amide* had m. p. 135° (from ethanol) (Found: C, 67·1; H, 6·2. $C_{17}H_{19}O_2NS$ requires C, 67·7; H, 6·35%).

*1,2,3,4-Tetrahydro-5-nitro-6-toluene-*p*-sulphonamidonaphthalene,* prepared similarly and crystallised from acetic acid, had m. p. 156° (Found: C, 59·0, H, 5·2. $C_{17}H_{18}O_4N_2S$ requires C, 59·0; H, 5·4%).

Nitrations of 6-acetamido-1,2,3,4-tetrahydronaphthalene. (a) In acetic anhydride. To the amide (1 g.) suspended in acetic anhydride (1 c.c.) was slowly added a mixture of nitric acid (*d* 1·42; 0·34 c.c., 1 mol.) and acetic anhydride (0·34 c.c.), the temperature being kept just

[2] Ingold, "Structure and Mechanism in Organic Chemistry," Bell and Sons, London, 1953, pp. 256—257, 261—264.
[3] Ward, Coulson, and Wells, *J.*, 1957, 4816.
[4] Schroeter, *Annalen*, 1922, **426**, 1.

below 50°. The next day the mixture was extracted with benzene (2 × 30 c.c.), and the extract dried (Na_2CO_3–Na_2SO_4) and concentrated to 20 c.c. This was then chromatographed on alumina (2·5 × 25 cm.) prepared in benzene–ethyl acetate (20 : 1, v/v), the same solvent being used for elution. The lower yellow band yielded 6-acetamido-1,2,3,4-tetrahydro-7-nitronaphthalene (0·52 g. ,42%), m. p. 132—133° (Van Rij *et al.* [5] gives m. p. 134—135°), and the upper yellow band gave the 5-nitro-isomer (0·47 g., 38%), m. p. 127° (Schroeter [4] gives 128—129°). Larger amounts of nitric acid produced some 6-acetamido-1,2,3,4-tetrahydro-5,7-dinitronaphthalene, which stayed at the top of the column and was eluted by ethyl acetate.

(b) In sulphuric–nitric acid. A solution of the amide (4·0 g.) in sulphuric acid (*d* 1·84; 42 c.c.) was treated with nitric acid (*d* 1·42; 1·3 c.c., 1 mol.) at −5°. After being kept for 10 min. at 0° the mixture was poured on ice (*ca.* 800 g.), and the solid product was collected, washed with water, and dried (4·87 g., 98%). Paper chromatography by the method of Franc and Latinák [6] showed that all three possible monitrated isomers were present. The R_F values for a run of 22 cm. at 20° were: 5-nitro 0·79, 7-nitro 0·64, 8-nitro 0·88. All three isomers gave black spots under ultraviolet light but when kept for several days the spot for the 8-nitro-isomer became violet. The mixed amides were crystallised from benzene (*ca.* 40 c.c.) which yielded pure 8-nitroamide (3·59 g.). Chromatography of the residual liquor on alumina gave in order of elution, the 8-, 7-, and 5-nitro-compound.

Mono- and di-nitration of 6-p-*toluenesulphonamido*-1,2,3,4-*tetrahydronaphthalene.* (a) Mononitration. The amide (1 g.) in acetic acid (30 c.c.) at 35° was treated with a crystal of sodium nitrite, then nitric acid (*d* 1·5; 0·14 c.c.). The next day the mixture was added to ice–water, and the solids were collected, washed with water, dried (1·12 g.), and chromatographed in benzene (25 c.c.) on alumina (2·5 × 25 cm.), prepared in benzene–ethyl acetate (2 : 1, v/v). Elution by the latter solvent removed a yellow band (A); another yellow band (B) was eluted by ethyl acetate; the residual yellow band (C) was separated from the column and extracted with methanol (Soxhlet). Band A was the 7-nitro-amide (0·46 g.), m. p. 144—145° (Kuhn *et al.*[7] give 146°). Band B was the 5-nitro-amide (0·61 g., 53%), m. p. 154—155°. Band C was 1,2,3,4-*tetrahydro*-5,7-*dinitro*-6-*toluene*-p-*sulphonamidonaphthalene* (0·04 g.), m. p. 226° (Found: C, 52·0; H, 4·3. $C_{17}H_{17}O_6N_3S$ requires C, 52·2; H, 4·35%).

(b) Dinitration. To the amide (1 g.) in acetic acid (30 c.c.) at 60° was added a crystal of sodium nitrite and nitric acid (*d* 1·5; 0·31 c.c., 2·2 mol.). The mixture was allowed to cool to room temperature and next day the solid product was collected. Further amounts were obtained by concentration of the filtrate (total yield, 0·99 g., 76%). This was the 5,7-dinitro-compound, m. p. and mixed m. p. 225°. The residual filtrate poured on ice gave only a small amount of low-melting material.

Nitration of 5-*acetamido*-1,2,3,4-*tetrahydronaphthalene and the preparation of* 5-*amino*-1,2,3,4-*tetrahydro*-6-*nitronaphthalene* (with A. W. Bamford). 5-Amino-1,2,3,4-tetrahydronaphthalene (60 g.) was refluxed with acetic acid (200 c.c.) and acetic anhydride (650 c.c.) for 30 min., then treated, at 30—35°, with nitric acid (*d* 1·42; 82·5 c.c.), and 30 min. later added to ice–water. The solid products were collected, washed with water, and dried (75 g., 79%). These mixed amides (25 g.) were refluxed with 1 : 1 v/v (1·5 l.) benzene–light petroleum (b. p. 60—80°) for 1 hr. Filtration of the hot solution gave a small residue (0·7 g.), probably 5-acetamido-1,2,3,4-tetrahydro-6,8-dinitronaphthalene. The cooled filtrate deposited 5-acetamido-1,2,3,4-tetrahydro-6-nitronaphthalene, m. p. 184° (from ethanol) (Schroeter [4] gives m. p. 184—185°) (42·5 g., 45%). This was hydrolysed by refluxing it with 2 : 1 : 1 v/v ethanol–water–sulphuric acid (*d* 1·84) for 3 hr.; the amine was obtained by pouring the solution into water (yield 98%). Concentration of the original filtrate gave a brown solid (22 g.) hydrolysis of which gave only tar. Diazotisation of the above amine by the method of Hodgson and Turner,[8] followed by decomposition of the diazonium solution by addition to iodine dissolved in aqueous potassium iodide (underlaid by chloroform), gave, from the chloroform layer, almost pure 1,2,3,4-*tetrahydro*-5-*iodo*-6-*nitronaphthalene* (*ca.* 85%); purified by chromatography on alumina in benzene and crystallised from ethanol, this had m. p. 60° (Found: C, 39·8; H, 3·5. $C_{10}H_{10}O_2NI$ requires C, 39·6; H, 3·3%).

[5] Van Rij, Verkade, and Wepster, *Rec. trav. chim.*, 1951, **70**, 236.
[6] Franc and Latinák, *Chem. Listy*, 1955, **49**, 872; cf. Ward and Johnson, *J.*, 1959, 487; Telesz and Johnson, *J. Soc. Dyers and Colourists*, 1958, **74**, 858.
[7] Kuhn, Vetter, and Rzeppa, *Ber.*, 1937, **70**, 1302.
[8] Hodgson and Turner, *J.*, 1943, 86.

XUM

1,2,3,4-*Tetrahydro-5-iodo-8-nitronaphthalene*, prepared similarly (*ca.* 90%), had m. p. 57° (Found: C, 39·8; H, 3·3%). The iodine atom in this compound proved inert when the compound was refluxed in ethanol with, *e.g.*, dimethylamine or di-*n*-butylamine.

The authors are indebted to the Department of Scientific and Industrial Research for a special grant.

LEICESTER COLLEGE OF TECHNOLOGY AND COMMERCE,
LEICESTER.

[*Received, April 3rd,* 1959.]

731. *The Periodate Oxidation of 2-Deoxyglycosides: Structure of 1-(2-Deoxy-D-galactosyl)benzimidazole.*

By R. J. FERRIER and W. G. OVEREND.

RECENTLY, syntheses have been described of 1-glycosylbenzimidazoles [1] and of 2-polyhydroxyalkylbenzimidazoles [2] derived from 2-deoxy-sugars. Attempts to establish the structures of these compounds by measuring periodate uptake were unsuccessful when the determinations were made by titrating with sodium arsenite the iodine liberated by excess of periodate.[3] Likewise, estimations on simple alkyl and aryl 2-deoxyglycosides resulted in values in excess of theory for the consumption of oxidant.[3] These anomalous results were obtained owing to iodination of the methylene group in the oxidation products. It has now been established that the spectrophotometric method for the determination of periodate as reported by Aspinall and Ferrier [4] can be used successfully with deoxy-sugar derivatives. Results obtained by this method are shown in the Experimental Section. It can be noted that methyl 2-deoxy-α-D-glucoside is oxidised more rapidly than methyl α-D-glucoside.

Condensation of crude tri-*O*-acetyl-2-deoxy-D-galactosyl bromide with benzimidazolylsilver in xylene gives, after deacetylation, a lævorotatory form (*A*) of 1-(2-deoxy-D-galactosyl)benzimidazole ($[\alpha]_D$ −18·9°). On the other hand the triacetyldeoxygalactosyl bromide with an excess of benzimidazole in dioxan at 100° affords finally only a small amount of compound (*A*), and the main product is a dextrorotatory isomer (*B*) ($[\alpha]_D$ +21·6°).[1] These compounds, which are interconvertible, were considered to be α- and β-isomers although the size of the sugar ring in each compound was not established. They were oxidised by 0·004M-periodate at 21°, and it was found by the spectrophotometric procedure that both consumed 1 mole of oxidant per mole of glycoside. (Control experiments indicated that a small correction for the absorption by the benzimidazole portion of the molecule was necessary.) By the oxidation of each compound negligible quantities of formaldehyde were produced. Consequently both isomers (*A*) and (*B*) possess a pyranosyl ring: this supports the contention that they are α- and β-isomers.

Experimental.—All compounds were oxidised with 1·5—2·0 molar equivalents of 0·004M-sodium periodate at 20—21°. Periodate uptake was followed spectrophotometrically by Aspinall and Ferrier's method: [4]

(i) *Methyl 2-deoxy-α-D-glucoside.*

Time (hr.)	0·33	1·0	2·0	3·5	6
Periodate uptake (mol.)	0·59	0·85	1·01	1·04	1·14

(ii) 1-(2-*Deoxy-D-galactosyl*)*benzimidazole* (B).

Time (hr.)	0·33	1·0	2·0	3·5
Periodate uptake (mol.)	0·91	0·96	1·08	1·11

(iii) 1-(2-*Deoxy-D-galactosyl*)*benzimidazole* (A).

Time (hr.)	0·25	1·0	2·0
Periodate uptake (mol.)	0·92	0·98	0·99

[1] Cleaver, Foster, and Overend, *J.*, 1959, 409.
[2] *Idem*, *J.*, 1957, 3961.
[3] Cleaver, Foster, Hedgley, and Overend, *J.*, 1959, 2578.
[4] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 1216.

XUM

The formaldehyde produced by the oxidation of isomers (*A*) and (*B*) was estimated by O'Dea and Gibbons's method [5] except that excess of periodate was destroyed with stannous chloride instead of lead dithionate. The complete oxidation of each compound yielded 0·08 mol. of formaldehyde per mol. of benzimidazole deoxyglycoside.

(iv) *Other derivatives.* Periodate uptake was estimated after 2 hours' oxidation.

Compound	Periodate uptake (mol.)	Theoretical uptake (mol.)
Methyl 2-deoxy-α-D-galactopyranoside	1·04	1·00
Methyl 2-deoxy-α-D-glucopyranoside	1·01	1·00
Phenyl 2-deoxy-α-D-glucopyranoside	1·00	1·00
Methyl α-D-glucopyranoside	0·6	2·0
2-Deoxy-D-glucitol	2·8	3·0

CHEMISTRY DEPARTMENT,
BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, April 6th,* 1959.]

[5] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.

---

732. p-*Bisphenylmercuribenzene.*

By M. MALNAR and D. GRDENIĆ.

IN connection with other work we needed *p*-bisphenylmercuribenzene. Of the several methods for its preparation we chose the Grignard reaction of *p*-bisbromomagnesiobenzene with phenylmercuric bromide.

The difficulty of obtaining the dimagnesium compound is already known.[1] We chose Houben's method [2] but later found that the amount of magnesium dissolved could be increased by prolonging the period of heating and by reducing the quantity of solvent. Nevertheless, the yield of *p*-bisphenylmercuribenzene was never higher than 16% of the theoretical amount. The main product was an insoluble polymer.

Experimental.—A solution of *p*-dibromobenzene (5·2 g.) in dry ether (15 ml.) was slowly added to magnesium turnings (1·08 g.) in stirred dry ether (15 ml.). The reaction was started with methyl iodide and thereafter maintained by the portionwise addition of half of the dibromobenzene solution. The other half was then added and the mixture refluxed for 24 hr. The solution was then diluted with ether (35 ml.), finely powdered phenylmercury bromide (15·8 g.) added, and the stirred mixture refluxed for 10 hr. After addition of water (50 ml.) and 10% hydrochloric acid (15 ml.) the cream-coloured precipitate was dried and extracted several times with hot toluene. From the toluene solution a yellowish powder was deposited (2·3 g.) which after recrystallization from toluene had m. p. 143° (Found: C, 35·0; H, 2·7; Hg, 63·4. $C_{18}H_{14}Hg_2$ requires C, 34·2; H, 2·2; Hg, 63·55%).

THE UNIVERSITY AND RUDJER BOŠKOVIĆ INSTITUTE,
ZAGREB, YUGOSLAVIA. [*Received, April 6th,* 1959.]

[1] Yoffe and Nesmeyanov, "A Handbook of Organomagnesium Compounds" (in Russian), Vol. I—III, The Academy of Sciences of the U.S.S.R., Leningrad, 1950; Lukeš and Prelog, *Chem. Listy*, 1930, **24**, 277; Millar and Heaney, *Quart. Rev.*, 1957, **11**, 109.
[2] Houben, *Ber.*, 1905, **38**, 3796.

XUM

733. *Aromatic Reactivity. Part VII.* Additivity of Effects of Methyl Substituents in Protodesilylation.*

By C. Eaborn and R. C. Moore.

We have measured the rates of cleavage of the tolyl- and xylyl-trimethylsilanes and of phenyl- and mesityl-trimethylsilane by aqueous-methanolic perchloric acid. Several acid concentrations must be used to cover the range of compounds, but by a stepwise procedure the reactivity, $k_{rel.}$, of each compound relative to that of phenyltrimethylsilane can be derived. The results are shown in the Table, which includes values of $k_{rel.}$(calc.) (*i.e.*, the reactivity of a xylyl or mesityl compound calculated on the assumption that the effects of the methyl groups, as revealed in the tolyl compounds, are additive). Agreement between $k_{rel.}$ and $k_{rel.}$(calc.) is excellent except for the 2,6-Me_2-, 2,4,6-Me_3-, and 2,3-Me_2-compounds, which are more reactive than expected because of release of steric strain on going from ground state to transition state.[1,2] In the case of the 2,3-Me_2-compound a " buttressing effect " is involved.[1]

The conclusions are very similar to those based on cleavage by toluene-*p*-sulphonic or hydrochloric acid in acetic acid–water.[1,2] †

Cleavage of substituted phenyltrimethylsilanes at 50·0°.

Subst.	$[HClO_4]$ [a] (M)	10^3k_1 (min.$^{-1}$)	$k_{rel.}$	$k_{rel.}$ (calc.)	Subst.	$[HClO_4]$ [a] (M)	10^3k_1 (min.$^{-1}$)	$k_{rel.}$	$k_{rel.}$ (calc.)
None ...	7·54	0·63	1	—	2,3-Me_2 ...	6·16	20·00	71·9	43·6
2-Me ...	7·54	11·50	18·3	—		3·08	2·86	—	—
	6·16	5·08	—	—	2,4-Me_2 ...	6·16	116	422	417
3-Me ...	7·54	1·50	2·38	—		3·08	16·8		
4-Me ...	6·16	6·35	22·8	—	2,6-Me_2 ...	3·08	138	3530	335
3,5-Me_2...	6·16	1·67	6·00	5·70		0·640	11·7	—	—
2,5-Me_2...	6·16	11·94	42·9	43·6	2,4,6-Me_3	0·640	176	53,000	7640
	3·08	1·68	—	—		0·103	21·4	—	—
3,4-Me_2...	6·16	15·61	56·1	54·3					
	3·08	2·19	—	—					

[a] Concn. of aqueous acid, 2 vol. of which were added to 5 vol. of a solution of the organosilane in methanol.

Experimental.—The xylyltrimethylsilanes, $Me_2C_6H_3{\cdot}SiMe_3$, were mainly prepared from the chloroxylenes, trimethylchlorosilane, and sodium in boiling toluene. After fractional distillation they had the following properties: 3,4-Me_2, b. p. 211·8°, n_D^{20} 1·4995; 2,3-Me_2, b. p. 218°, n_D^{20} 1·5106; 2,4-Me_2, b. p. 215—216°, n_D^{20} 1·5050; 2,6-Me_2, b. p. 224—226°, n_D^{20} 1·5179; 2,5-Me_2, b. p. 208—209°, n_D^{20} 1·5056. The 3,5-Me_2-compound, b. p. 210°, n_D^{20} 1·4950, and the 2,4,6-Me_3-compound, b. p. 237°, were prepared from the aryl bromides. The mesityl compound could not be obtained free from an impurity, but this did not interfere with the rate measurements, identical rates being obtained with samples from different preparations and from different fractions in the distillations.

The method of measuring rates has been described.[3] The molar concentration of the silane in methanol (before addition of acid) and (in parentheses) the wave lengths (in mμ) used were as follows: 2,4,6-Me_3, 0·0037 (277); 3,5-Me_2, 0·0022 (279); 2,5-Me_2, 0·0016 (280); 3,4-Me_2, 0·003 (277); 2,3-Me_2, 0·003 (277); 2,6-Me_2, 0·003 (278); *o*-Me, 0·01 (278); *m*-Me, 0·01 (278); *p*-Me, 0·01 (273); unsubstituted compound, 0·012 (270).

We thank Imperial Chemical Industries Limited for a grant towards the cost of chemicals.

The University, Leicester. [*Received, April 7th*, 1959.]

* Part VI, *J.*, 1959, 3034.

† In absence of information on cleavage of tolyltrimethylsilanes in such media, de la Mare analysed data for xylyltrimethylsilanes by use of figures for bromination of toluene by a positive species, and concluded wrongly that the 2,3-Me_2-compound was only normally reactive.[2]

[1] Benkeser and Krysiak, *J. Amer. Chem. Soc.*, 1954, **76**, 6353; Benkeser, Hickner, Hoke, and Thomas, *ibid.*, 1958, **80**, 5289.

[2] de la Mare, " Progress in Stereochemistry," edited by Klyne and de la Mare, Butterworths Scientific Publications, London, 1958, Vol. II, pp. 73—75.

[3] Eaborn, *J.*, 1956, 4858.

XUM

734. *Substituent Effects in Fluorene Compounds. Part II.* Substituted 9-Fluorenones in Oxime Formation.*

By J. D. Dickinson and C. Eaborn.

We have measured the rates of reaction of some 2- and 3-substituted 9-fluorenones with excess of hydroxylamine hydrochloride in " 70% methanol " containing sodium acetate and acetic acid. The results are shown in the Table as pseudo-first-order rate constants k_1. The rates, $k_{rel.}$, relative to that of the unsubstituted compound are also listed, along with the apparent activation energies, E, derived from measurements at 50·0° and 40·0°.

Substituent	2-CN	2-NO_2	2-Br	2-NHAc	2-MeO	None
10^2[NH_2·OH,HCl] (M) [a]	9·20	4·56	4·56	9·20	9·20	4·56
10^3k_1 (50°) (min.$^{-1}$)	3·46	1·13	0·87	1·94	1·88	0·694
$k_{rel.}$	1·99	1·63	1·25	1·11	1·08	1
E (kcal./mole)	10·1	10·3	8·5	9·7	9·9	9·0

Substituent	None	2-HO	2-Me	3-Br	3-Me	3-MeO
10^2[NH_2·OH,HCl] (M) [a]	9·20	9·20	9·20	9·20	9·20	9·20
10^3k_1 (50°) (min.$^{-1}$)	1·74	1·74	1·74	1·71	1·24	0·590
$k_{rel.}$	1	1·00	1·00	0·98	0·71	0·339
E (kcal./mole)	—	10·1	10·4	9·6	10·0	11·4

[a] Calc. by assuming volume additivity on mixing of aqueous and methanolic solutions (see Experimental section).

The variations in E are too small to warrant discussion. The pattern of substituent effects is very similar to that observed for benzophenones,[1] if 2- and 3-substituents in fluorenone are regarded as equivalent to *meta*- and *para*-substituents, respectively, in benzophenone. In neither case do the simple Hammett σ-constants represent the effects of the substituents, for reasons we have previously discussed.[1] A point of interest is that the 2-methoxy-group activates fluorenone slightly, while the 2-methyl group deactivates slightly and the 3-methoxy-group more strongly. It thus seems that tautomeric eletron-release from the 2-methoxy-group is not significantly transmitted to the 9-position through the unsubstituted ring (see Part I).

Fluorene is 16·7 times as reactive as benzophenone in oxime formation at 50°. This is consistent with Price and Hammett's observation that the more rigid the structure of a ketone the more reactive it is in carbonyl-addition reactions,[2] but it should be noted that the reactivity difference largely arises from a lower activation energy in the case of fluorenone, not from a more favourable activation entropy as might be expected if rigidity is the important factor. With both fluorenones and benzophenones the reaction is facilitated by electron-withdrawing substituents, and the higher reactivity of fluorenone probably originates in the well-known electron affinity of the cyclopentadiene system.

Experimental.—The preparation of the fluorenones has been described.[3]

Three volumes of stock aqueous hydroxylamine hydrochloride (0·613 or 0·304M) were made up to 10 volumes with methanol. The solution thus obtained was added to an equal volume of a solution of the fluorenone (of concentration shown in the Table below) in " 70% methanol "

Subst.	Concn. (g./l.)	λ (mμ)	Subst.	Concn. (g./l.)	λ (mμ)	Subst.	Concn. (g./l.)	λ (mμ)
H	0·47	330	2-Me	0·23	330	2-NHAc ...	0·48	380
2-Br	0·81	360	2-HO	0·42	330	2-CN	0·17	333
2-NO_2 ...	0·070	370	3-Me	0·13	335	3-Br	0·28	335
2-MeO ...	0·54	330	3-MeO ...	0·087	345	—	—	—

(3 vol. of water made up to 10 vol. with methanol) containing sodium acetate and glacial acetic acid (both 0·2M). The reaction was followed spectrophotometrically at the wavelengths (λ)

* Part I, *J.*, 1959, 3574.

[1] Dickinson and Eaborn, *J.*, 1959, 3036.
[2] Price and Hammett, *J. Amer. Chem. Soc.*, 1941, **63**, 2387.
[3] Dickinson and Eaborn, *J.*, 1959, 2337.

shown in the Table, as previously described.[1] Rate constants were reproducible to within 2%.

In the medium used with benzophenone (for which the aqueous hydroxylamine hydrochloride was 4·20M) [1] the rate constant for fluorenone was 0·150 min.$^{-1}$ at 50°.

THE UNIVERSITY, LEICESTER. [*Received, April 10th,* 1959.]

---

735. *Synthesis of α-Azido-γ-butyrolactone and its Reduction to α-Amino-compounds.*

By MAX FRANKEL, Y. KNOBLER, and T. SHERADSKY.

γ-BUTYROLACTONE has been used extensively in the synthesis of α-amino-acids, and several methods have been found to introduce into it the α-amino-group.

Snyder *et al.*[1] worked out a procedure for the α-amination of butyrolactone by way of α-acetyl-γ-butyrolactone and α-hydroxyimino-γ-butyrolactone, and for hydrogenation of the last to 2,5-di-(2-hydroxyethyl)-3,6-dioxopiperazine.

Livak *et al.*[2] prepared α-bromo-γ-butyrolactone and introduced the α-amino-group by means of aqueous ammonia, with α-amino-γ-hydroxybutyramide as intermediate which has to be hydrolysed. The α-amino-γ-butyrolactone was isolated as hydrobromide in the laborious process of separating it from inorganic salts formed, or it was converted into a water-insoluble derivative, the α-benzamido-γ-butyrolactone[3] or the α-benzyloxycarbonylamino-γ-butyrolactone.[3]

Introduction of the α-amino-group without opening of the lactone ring was effected by treating α-bromo-γ-butyrolactone with a molar quantity of potassium phthalimide,[4,5] and the water-insoluble α-phthalimido-γ-butyrolactone was obtained directly.

In continuation, the present work utilises the azido-group for the α-amination of γ-butyrolactone. α-Bromo-γ-butyrolactone with sodium azide in ethanolic solution gave α-azido-γ-butyrolactone in 70—80% yield. The azido-group was transformed into the α-amino-group by acidolytic or catalytic reduction; this was effected, according to the conditions employed, with conservation or opening the lactone ring.

Treating α-azido-γ-butyrolactone with 24% solution of hydrogen bromide in acetic acid precipitated α-amino-γ-butyrolactone hydrobromide in 70% yield. Similar treatment with hydrogen iodide gave the hydriodide, but yields were only 40—50%.

Catalytic reduction of α-azido-γ-butyrolactone with palladium black in the presence of hydrogen chloride afforded α-amino-γ-butyrolactone hydrochloride in 75% yield; in ethanol–water, in the presence of a base, the simultaneous reduction and opening of the lactone ring led to homoserine (α-amino-γ-hydroxybutyric acid); with sodium hydroxide as base the yield was only about 40%, with triethylamine 80%.

When catalytic reduction of the azido-lactone in absolute ethanolic solution was followed by long refluxing the aminolactone dimerised,[2,3,6] giving 2,5-di-(2-hydroxyethyl)-3,6-dioxopiperazine in 60% yield.

Unlike other α-aminated γ-butyrolactones, *e.g.*, α-benzamido- and α-phthalimido-γ-butyrolactone which are converted into α-amino-γ-iodobutyric acid hydriodide by refluxing with concentrated hydriodic acid,[7] the α-azido-γ-butyrolactone gave the corresponding γ-iodo-compound in a very poor yield. Treatment of the α-azido-γ-butyrolactone with amino-acid derivatives failed to yield a peptide linkage, as is given by α-benzamido- and α-benzyloxycarbonylamino-γ-butyrolactone.[7]

[1] Snyder, Andreen, Cannon, and Peters, *J. Amer. Chem. Soc.*, 1942, **64**, 2082.
[2] Livak, Britton, Vanderweele, and Murray, *ibid.*, 1945, **67**, 2218.
[3] Knobler and Frankel, *J.*, 1958, 1629.
[4] Frankel, Knobler, and Sheradsky, *Bull. Res. Council Israel*, 1958, **7**, *A*, 173.
[5] Talbot, Gaudry, and Berlinguet, *Canad. J. Chem.*, 1958, **36**, 593.
[6] Fischer and Blumenthal, *Ber.*, 1907, **40**, 106.
[7] Unpublished results.

XUM

All these preparations, including those of α-azido-γ-butyrolactone, the salts of α-amino-γ-butyrolactone, homoserine, and 2,5-di-(2-hydroxyethyl)-3,6-dioxopiperazine, are very convenient and proceed smoothly.

Experimental.—*α-Azido-γ-butyrolacone.* α-Bromo-γ-butyrolactone (33 g.) and sodium azide (14·5 g.) were refluxed in ethanol (200 ml.) for 5 hr., and the solution was filtered and concentrated *in vacuo*. Water (100 ml.) was added to the residue, and the lower layer was taken up in chloroform (70 ml.). The aqueous layer was extracted twice with chloroform (70 ml.), and the combined chloroform extracts were washed with water, dried (Na_2SO_4), and evaporated. The *azido-lactone* (16·8 g. 67%) had b. p. 83—85°/0·3 mm., n^{20} 1·4827, d^{20} 1·3861 (Found: C, 38·0; H, 4·1. $C_4H_5O_2N_3$ requires C, 37·8; H, 3·9%).

During distillation the azide may explode if the bath-temperature exceeds 150°. Slight decomposition occurs on prolonged storage.

Undistilled azido-lactone can be used for the following steps, but yields are lower.

α-Amino-γ-butyrolactone hydrobromide. To α-azido-γ-butyrolactone (6·35 g.) a 24% solution of dry hydrogen bromide in acetic acid (100 ml.) was added, in portions with shaking. The temperature rose to 50—60° and evolution of nitrogen occurred. Then the mixture was stirred for 4 hr., during which the amino-lactone hydrobromide was precipitated. Next morning it was collected and washed with ether. A second crop was obtained by evaporating the filtrate *in vacuo* and washing the residue with ethanol and ether. The lactone (6·8 g., 70%) melted at 223—224° (Found: N, 7·7; Br, 44·4. Calc. for $C_4H_6O_2NBr$: N, 7·7; Br, 43·9%).

α-Amino-γ-butyrolactone hydrochloride. α-Azido-γ-butyrolactone (3·2 g.) was dissolved in acetic acid (40 ml.), and hydrochloric acid (5 ml.) and palladium black (50 mg.) were added. The mixture was hydrogenated at 30—35°/2 atm. for 4 hr. The catalyst was removed and the acetic acid evaporated *in vacuo*. The oily residue crystallised on addition of a little dry ethanol. It (2·75 g. 78%) melted at 199—201° (Found: N, 9·9. Calc. for $C_4H_8O_2NCl$: N, 10·2%).

α-Amino-γ-hydroxybutyric acid (homoserine). α-Azido-γ-butyrolactone (6·35 g.) in ethanol (20 ml.) and water (20 ml.) containing triethylamine (5 ml.) and palladium black (100 mg.) was hydrogenated. The catalyst was removed, and acetone (100 ml.) was added. The precipitated acid (4·9 g. 82%) recrystallised from water–acetone and melted at 184—185° [Found: N (Van Slyke), 11·7. Calc. for $C_4H_9O_3N$: N, 11·8%].

2,5-Di-(2-hydroxyethyl)-3,6-dioxopiperazine. α-Azido-γ-butyrolactone (6·35 g.) in absolute ethanol (50 ml.) with palladium black (100 mg.) was hydrogenated. The catalyst was removed, and the ethanolic solution was refluxed for 24 hr. The product (3 g., 60%) crystallised (m. p. 185—186°; ninhydrin reaction negative) [Found: N (Kjeldahl), 13·6; N (Van Slyke), 0·0. Calc. for $C_8H_{14}O_4N_2$: N, 13·9%].

Department of Organic Chemistry, The Hebrew University, Jerusalem, Israel. [*Received, April 23rd*, 1959.]

736. *The Reactions of Boron Halides with Anhydrous Sulphuric Acid: Boron Tri(hydrogen sulphate) and Tetra(hydrogen sulphato)boric Acid.*

By N. N. Greenwood and A. Thompson.

It has been suggested [1] that boron trifluoride forms a 1 : 1 addition compound with sulphuric acid but there is no evidence for this in the literature. Davy [2] observed that sulphuric acid absorbed 50 times its volume of gaseous boron trifluoride, which corresponds to the composition $H_2SO_4,0{\cdot}123BF_3$, and Paushkin [3] formulated the saturated solution as $BF_3 + 2\frac{1}{2}H_2SO_4$, *i.e.*, $H_2SO_4,0{\cdot}4BF_3$. We find that a saturated solution of boron trifluoride in anhydrous sulphuric acid contains less than 3 moles % of the gas, *i.e.*, $H_2SO_4,0{\cdot}028BF_3$, and explain the earlier observations as due to the presence of water in the sulphuric acid. Thus, Davy's acid had a specific gravity of 1·85, corresponding to

[1] Booth and Martin, "Boron Trifluoride and its Derivatives," John Wiley and Sons, Inc., 1949, pp. 56, 168.
[2] Davy, *Phil. Trans.*, 1812, **102**, 352.
[3] Paushkin, *Zhur. priklad. Khim.*, 1948, **21**, 1199.

XUM

approximately 98% by weight of sulphuric acid or, on a molar basis, $H_2SO_4,0{\cdot}11H_2O$; formation in solution of the 1 : 1 compound BF_3,H_2O would therefore account for almost all the gas absorbed. Likewise, the acid used in Paushkin's experiments was stated to be 94—100%.[4] The lower value is equivalent to $H_2SO_4,0{\cdot}35H_2O$, so that combination of boron trifluoride with this water again accounts for most of the gas absorbed. The absence of appreciable interaction between boron trifluoride and sulphuric acid is surprising in view of (*a*) the ease with which the related electron acceptor sulphur trioxide dissolves to give oleums from which pyrosulphuric acid, H_2SO_4,SO_3, can be crystallized, and (*b*) the existence of compounds such as M_2SO_4,BF_3 analogous to the pyrosulphates.[5]

The conductivity of anhydrous sulphuric acid at 25° is $1{\cdot}044 \times 10^{-2}$ ohm^{-1} cm.$^{-1}$.[6] Using acid of conductivity $4{\cdot}36 \times 10^{-2}$ ohm^{-1} cm.$^{-1}$, Topchiev and Paushkin found that boron trifluoride lowered this conductivity to $3{\cdot}57 \times 10^{-2}$ ohm^{-1} cm.$^{-1}$, a factor of 0·82.[4] In our experience the effect is even more marked with pure acid, and a saturated solution (2·9 moles % of boron trifluoride) had a conductivity only 0·53 that of the solvent acid. This reduction in conductivity is presumably due to a partial suppression of the proton-switch conduction mechanism in a manner similar to that encountered in the boron trifluoride–phosphoric acid system.[7]

Boron trichloride, in contrast to the trifluoride, reacts vigorously with anhydrous sulphuric acid according to the equation

$$BCl_3 + 3H_2SO_4 = B(HSO_4)_3 + 3HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Boron tri(hydrogen sulphate) was obtained as a white deliquescent powder which did not melt when heated in a sealed tube to 240°. It was readily soluble in anhydrous sulphuric acid and an equimolar solution set to a moist solid at room temperature:

$$B(HSO_4)_3 + H_2SO_4 = HB(HSO_4)_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

A solid of the same composition was obtained directly by reaction of sulphuric acid with the calculated amount of boron trichloride:

$$BCl_3 + 4H_2SO_4 = HB(HSO_4)_4 + 3HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The compound decomposed into a liquid with some evolution of gas when heated. In this instability it resembles other anhydrous acids of tetraco-ordinated boron, *e.g.*, fluoroboric acid, HBF_4, and boron trifluoride monohydrate, HBF_3OH.

No reaction between boron trichloride and sulphuric acid has been reported previously but, when the gas was condensed with sulphur trioxide at −80°, an unstable compound $BCl_3,2SO_3$ was formed which can be formulated as di(chlorosulphonato)boron chloride, $BCl(O{\cdot}SO_2Cl)_2$.[8] Boron tri(hydrogen sulphate) has been reported as the product of the reaction of boric oxide with sulphuric acid.[9] The white, hygroscopic solid had the correct analysis but melted at about 215° in contrast to our product which was infusible at 240°. The compound has also been postulated to exist in dilute solutions of boric oxide in sulphuric acid [10] but more recent cryoscopic and conductometric work on very dilute solutions of boric oxide and boric acid in sulphuric acid and oleum favours the formation of tetra(hydrogen sulphato)boric acid in these solutions.[11] The compound was not isolated at that time however.

Experimental.—Boron trifluoride (Imperial Smelting Co.) and boron trichloride (B.D.H.) were used after a preliminary fractionation. The preparation of anhydrous sulphuric acid [6] and the design of the conductivity cell [12] have previously been described.

[4] Topchiev, Paushkin, Vishnyakova, and Kurashov, *Doklady Akad. Nauk, S.S.S.R.*, 1951, **80**, 611.
[5] Baumgarten and Müller, *Ber.*, 1936, **69**, 2688; Baumgarten and Hennig, *ibid.*, 1939, **72**, 1743.
[6] Greenwood and Thompson, *J.*, 1959, 3474.
[7] *Idem*, *ibid.*, p. 3493.
[8] Luchinski, *Zhur. obshchei Khim.*, 1941, **11**, 884.
[9] D'Arcy, *J.*, 1889, **55**, 155.
[10] Hantzsch, *Z. phys. Chem.*, 1908, **61**, 257.
[11] Flowers, Gillespie, and Oubridge, *J.*, 1956, 1925.
[12] Greenwood, Martin, and Emeléus, *J.*, 1951, 1328.

XUM

Boron tri(hydrogen sulphate). Excess of boron trichloride was condensed at −80° from a vacuum line on to a known weight of sulphuric acid in a reaction vessel fitted with a spring-loaded tap. The contents were allowed to warm slowly to room temperature and, as the sulphuric acid melted, a highly exothermic reaction ensued with considerable frothing. The reaction vessel was then evacuated and reweighed. Equation 1 requires that 1 g. of H_2SO_4 yield 1·027 g. of $B(HSO_4)_3$; our yield was 1·027 g. The gases evolved in the reaction contained no sulphur and, after fractionation, proved to be hydrogen chloride (M, 34·9—38·0) and the unchanged excess of boron trichloride. The solution obtained by hydrolysis of the *product* contained boron and sulphate but no chloride. It was titrated with 0·1N-sodium hydroxide to the methyl orange end-point to determine sulphuric acid and then, in the presence of mannitol, to the phenolphthalein end-point to determine boric acid [Found: B, 3·6; SO_4, 93·2. $B(HSO_4)_3$ requires B, 3·6; SO_4, 95·4%].

Tetra(hydrogen sulphato)boric acid. Addition of an equimolar amount of boron tri(hydrogen sulphate) to anhydrous sulphuric acid resulted in a moist solid of indefinite m. p. which decomposed on being heated. Reaction of one mole of boron trichloride with four moles of sulphuric acid gave the theoretical weight of *product* according to equation (3); it contained only a trace of chlorine [Found: B, 2·76; SO_4, 94. $HB(HSO_4)_4$ requires B, 2·77; SO_4, 96%].

THE UNIVERSITY, NOTTINGHAM. [*Received, April 29th*, 1959.]

---

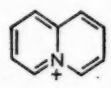
737. *A Molecular Orbital Calculation of the Ultraviolet Absorption Spectrum of the Quinolizinium Cation.*

By T. E. PEACOCK.

THE quinolizinium cation (I) and naphthalene are isoelectronic and, because they possess the same framework it is reasonable to expect that their electronic spectra will be related.

The electronic spectrum has been calculated by the methods of previous papers,[1-3] in which we use the SCF (self-consistent field) molecular orbitals of the hydrocarbon parent (*i.e.*, naphthalene) in order to calculate the spectrum of the heterocyclic derivative.

The spectrum of naphthalene, which has the symmetry D_{2h}, has already been discussed in detail.[2,4] The energies of its two highest occupied and two lowest unoccupied SCF molecular orbitals, and their symmetry symbols, are:

(I) 

The quinolizinium cation has the reduced symmetry C_{2v}. The ground state function Φ_0 and the functions of the excited configurations $\Phi(A \longrightarrow A')$, $\Phi(B \longrightarrow B')$, $\Phi(A \longrightarrow B')$, $\Phi(B \longrightarrow A')$ are grouped according to symmetry under C_{2v} in Table 1. Here, for instance, $\Phi(A \longrightarrow A')$ is the singlet function in which the configuration is $(A)^1(A')^1$ instead of $(A)^2$.

TABLE 1.

Symmetry	*A*	*B*
Function	Φ_0	$\Phi(A \longrightarrow B')$
	$\Phi(B \longrightarrow B')$	$\Phi(B \longrightarrow A')$
	$\Phi(A \longrightarrow A')$	

Since there are excited functions of the same symmetry as the ground-state function, mixing will be allowed and is adequate to describe the effect of the substituent on the charge distribution without any revision of the basic orbitals.[1]

[1] McWeeny, *Proc. Phys. Soc.*, 1957, *A*, **70**, 593.
[2] Peacock, *Proc. Phys. Soc.*, 1957, *A*, **70**, 645.
[3] Peacock, *J.*, 1959, 2308.
[4] Peacock, *J.*, 1959, 3421.

The general interpretation of the so-called α, *p*, β, and β′ bands of an alternant hydrocarbon [5] and its heterocyclic derivatives [3,6,7] in terms of the mixing of the configurational functions discussed above, is now well known.

The value of the framework parameter for the doubly-charged nitrogen ion was chosen to reproduce Brown and Penfold's [8] charge distribution for $CH_2{\cdot}NH_2^+$: this value is 3·0β where β is the SCF value of the C–C resonance integral in benzene. At first sight this value is somewhat high, but this is due to the atom's being doubly ionized and requiring a substantial proportion of the π electrons (about 1·5) in order to screen its large framework charge. This value agrees closely with that determined experimentally.[9] The other parameters and the two-electron integrals were given the same values as in previous work.[2,6]

Results.—The calculated transition energies and oscillator strengths for the quinolizinium ion are given in Table 2, and the wave functions for the ground state and excited states in Table 3.

TABLE 2.

State and symmetry	Transition energy ($\tilde{\nu}$)	Predicted oscillator strength	Observed band ($\tilde{\nu}$)	State and symmetry	Transition energy ($\tilde{\nu}$)	Predicted oscillator strength	Observed band ($\tilde{\nu}$)
	Naphthalene				Quinolizinium *		
$\alpha(B_3)$	35,900	0	32,300	$\alpha(B)$	34,900	0·314	30,300
$p(B_2)$	36,600	0·208	36,500	$p(A)$	41,300	0·228	44,000
$\beta(B_3)$	51,000	2·213	45,200	$\beta(B)$	60,700	2·160	
$\beta'(B_2)$	53,700	1·040	59,700	$\beta'(A)$	63,000	1·200	

* Experimental values taken from Jones and Glover.[10]

TABLE 3.

$$\Psi_0 = 0{\cdot}960\,\Phi_0 - 0{\cdot}100\,\Phi(A \longrightarrow A') + 0{\cdot}257\,\Phi(B \longrightarrow B')$$
$$\Psi_\alpha = 0{\cdot}951\,\Phi(A \longrightarrow B') - 0{\cdot}310\,\Phi(B \longrightarrow A')$$
$$\Psi_p = -0{\cdot}003\,\Phi_0 + 0{\cdot}928\,\Phi(A \longrightarrow A') + 0{\cdot}371\,\Phi(B \longrightarrow B')$$
$$\Psi_\beta = 0{\cdot}310\,\Phi(A \longrightarrow B') + 0{\cdot}951\,\Phi(B \longrightarrow A')$$
$$\Psi_{\beta'} = -0{\cdot}278\,\Phi_0 - 0{\cdot}341\,\Phi(A \longrightarrow A') + 0{\cdot}898\,\Phi(B \longrightarrow B')$$

Discussion.—The results account satisfactorily for the observed shifts and intensity changes of the main bands:

α *Band.* Theory predicts a bathochromic shift of 1000 $\tilde{\nu}$, which compares with the experimentally determined shift of 2000 $\tilde{\nu}$ (the agreement is quite good bearing in mind the difficulties which occur in determining the centre of the observed bands). The intensity is much higher than in naphthalene and this is predicted.

p Band. A hypsochromic shift of 4700 $\tilde{\nu}$ is predicted. The observed value is 7500 $\tilde{\nu}$. Again bearing in mind the uncertainty of the experimental value the agreement is quite good. The intensity of this band is predicted to be almost unchanged on substitution, which is observed.

In the quinolizinium ion the α and *p* bands are predicted to have comparable intensities—in contrast with the situation in naphthalene. This is in fact observed.

β *and* β′ *Bands.* These are predicted to occur at 60,700 $\tilde{\nu}$ and 63,000 $\tilde{\nu}$ and are as yet unobserved.

The author thanks Dr. R. McWeeny for his interest and the Ramsay Memorial Fellowship Trust for a Fellowship.

UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE, KEELE. [*Received, May 4th,* 1959.]

[5] Dewar and Longuet-Higgins, *Proc. Phys. Soc.*, 1954, *A*, **67**, 795.
[6] McWeeny and Peacock, *Proc. Phys. Soc.*, 1957, *A*, **70**, 41.
[7] Peacock, *Nature*, 1957, **179**, 684.
[8] Brown and Penfold, *Trans. Faraday Soc.*, 1957, **53**, 397.
[9] Mason, *J.*, 1958, 674.
[10] Jones and Glover, *J.*, 1958, 3021.

XUM

738. *Pyrimidine Reactions. Part II.* 2-Ethoxy-4-, and 4-Ethoxy-2-hydroxy-5-nitropyrimidine.*

By D. J. Brown.

2,4-Dichloro-5-nitropyrimidine [1] was converted by sodium ethoxide in anhydrous ethanol into 2,4-diethoxy-5-nitropyrimidine. This product corresponds to that made by nitrating 2,4-diethoxypyrimidine [2] and by other means.[3] When one mol. of water was initially present in the ethanol used, little diethoxynitropyrimidine resulted, but in its place there appeared two isomeric ethoxyhydroxypyrimidines and a little 5-nitrouracil. The best yield of the isomers was obtained by using 2·8 moles of sodium ethoxide per mole of dichloro-compound, and almost the same mixture resulted by similar partial hydrolysis of the diethoxy-derivative in the presence of 1 mol. of sodium ethoxide.

The structure of each isomer was found by amination. The 4-ethoxy-compound gave 5-nitrocytosine, and the 2-ethoxy-compound gave 5-nitroisocytosine. These amines were identified with authentic materials [4,5] by paper chromatography, pK_a determination, and ultraviolet and infrared spectra.

Inspection of the Table of spectra, along the lines now familiar from work by Marshall and Walker [6] and others,[7,8] suggests that 5-nitrouracil exists in aqueous solution predominantly as 1,2,3,4-tetrahydro-5-nitro-2,4-dioxopyrimidine.

5-Nitropyrimidine derivative	pK_a, spread, and concn.	pH	Ultraviolet spectra $\lambda_{max.}$ (mμ)	log ε
2,4-Diethoxy	—	7·0	296, 251	3·96, 3·78
2-Ethoxy-4-hydroxy	—	2·5	314, 238,[a] 225 [a]	3·89, 3·76, 3·83
anion	4·88 ± 0·05 (M/400)	7·0	341, 250,[a] 230	3·97, 3·74, 3·95
4-Ethoxy-2-hydroxy	—	4·5	298, 260	3·88, 3·90
anion	*ca.* 6·6 (M/400)	9·5	335, 266, 232	4·14, 3·61, 3·76
2,4-Dihydroxy [b]	—	3·3	298, 237	3·95, 3·82
anion	5·55 ± 0·03 (M/1000) [c]	7·7	341, 258, 229	4·13, 3·68, 3·78
dianion	11·3			
2-Amino-4-hydroxy	—	4·5	338, 254, 232	4·15, 3·70, 3·72
anion	6·70 ± 0·02 (M/1000)	9·5	353, 245	4·10, 3·75
4-Amino-2-hydroxy	—	5·0	317, 251,[a] 223	3·94, 3·90. 4·18
anion	7·34 ± 0·03 (M/1000)	9·5	353, 253, 214	4·21, 3·78, 4·06
1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo [d]	—	7·0	309, 239	3·95, 3·79

[a] Inflexion. [b] Prep.: see ref. 9. [c] Cf. ref. 10: 5·3 and 11·7 by spectrophotometric means. [d] Prep.: see ref. 11.

Experimental.—*2,4-Diethoxy-5-nitropyrimidine.* 2,4-Dichloro-5-nitropyrimidine [1] (1 g.) and sodium ethoxide [from sodium (0·3 g.) and anhydrous ethanol (20 ml.)] were kept at 25° for 2 hr. Carbon dioxide was introduced, and the filtered solution evaporated to dryness in a vacuum. Sublimation (45°/0·05 mm.) of the residue gave 53% of the product, m. p. 42—3° (lit., 45°) (Found: C, 45·2; H, 5·15; OEt, 41·2. Calc. for $C_8H_{11}O_4N_3$: C, 45·1; H, 5·2; OEt, 42·2%).

2-Ethoxy-4- and 4-ethoxy-2-hydroxy-5-nitropyrimidine. 2,4-Dichloro-5-nitropyrimidine (5·82 g.) and sodium ethoxide [from sodium (1·93 g.) and anhydrous ethanol (140 ml.)] with water (0·54 ml.) were refluxed for 20 min. The filtered solution was evaporated to dryness under reduced pressure at 30°, and the solid dissolved in hot ethanol (85 ml.). After refrigeration for

* Part I, *J.*, 1956, 2312.

[1] Whittaker, *J.*, 1951, 1565.
[2] Rabinowitz and Gurin, *J. Amer. Chem. Soc.*, 1953, **75**, 5758.
[3] Takahashi, Naito, and Inoue, *Chem. Pharm. Bull.* (*Japan*), 1958, **6**, 334.
[4] Johns, *Amer. Chem. J.*, 1911, **45**, 79.
[5] Johnson and Johns, *Amer. Chem. J.*, 1905, **34**, 554.
[6] Marshall and Walker, *J.*, 1951, 1004.
[7] Brown and Short, *J.*, 1953, **331**.
[8] Albert and Barlin, *J.*, 1959, in the press.
[9] Brown, *J. Appl. Chem.*, 1952, **2**, 239.
[10] Shugar and Fox, *Biochim. Biophys. Acta*, 1952, **9**, 199.
[11] Brown, Hoerger, and Mason, *J.*, 1955, 211.

at least 1 day, the solid was dissolved in water (16 ml.) at 40°, the solution adjusted to pH 2—3, and the product (1·1 g.) recrystallised from water (16 parts) to give colourless needles of the *2-ethoxy-isomer*, m. p. 165—166° (Found: C, 38·7; H, 3·6; OEt, 24·8. $C_6H_7O_4N_3$ requires C, 38·9; H, 3·8; OEt, 24·35%). The residue from evaporation of the ethanolic filtrate was triturated with water (12 ml.). Sublimation (45°/0·05 mm.) of the insoluble material gave the diethoxy-derivative (1·4 g.), m. p. 42—43°. Adjustment of the aqueous solution to pH 2—3, and recrystallization of the resulting solid from water (40 ml.), gave irregular plates (0·86 g.) of the *4-ethoxy-isomer*, m. p. 198—199° (Found: C, 38·9; H, 3·7; OEt, 24·8%).

Partial hydrolysis of 2,4-diethoxy-5-nitropyrimidine. The 2,4-diethoxy-compound (6·4 g.) was treated as above for 30 min., except that sodium (0·69 g.) was used. There resulted 2-ethoxy-isomer (1·6 g.), 4-ethoxy-isomer (0·95 g.), and unchanged material (0·03 g.).

5-Nitrocytosine and 5-nitroisocytosine. Each ethoxy-isomer (0·5 g.) was heated at 100° for 1 hr. with 6·5% alcoholic ammonia (4 ml.). After evaporation to dryness, the solid was triturated with 7·5N-acetic acid (5 ml.) to free the nitrocytosine (85%) and nitroisocytosine (50%), which recrystallised from water (respectively 350 and 80 parts).

I thank Mr. J. Harper for painstaking experiments, Mr. F. Robinson and Mr. D. Light for physical measurements, and Dr. J. E. Fildes and staff for analyses.

DEPARTMENT OF MEDICAL CHEMISTRY, AUSTRALIAN NATIONAL UNIVERSITY,
CANBERRA, AUSTRALIA. [*Received, May 19th*, 1959.]

---

739. *The Stability Constants of Some Metal Chelates of* ortho-*Aminophenols.*

By PETER SIMS.

IT has been suggested [1] that certain *ortho*-aminophenols are carcinogenic because of their ability to chelate with metals in the body. An attempt has been made, therefore, to measure the stability constants of some of these compounds: 3-hydroxyanthranilic acid and 2-amino-4,5-dimethylphenol (which are known carcinogens [1,2]) and 2-aminophenol (which is not a carcinogen).

Albert's methods [3,4] for the calculation of the stability constants have been applied to those parts of the titrations where consistent results were obtained. Because of the low solubilities of the aminophenols and of the chelate complexes in water, titrations were carried out on 0·001M solutions of the aminophenols (or of their hydrochlorides) but even

Stability constants of chelates of o-*aminophenols* (*at* 20°).

			Cu^{2+}		Fe^{2+}	Ni^{2+}		Co^{2+}	Cd^{2+}	Mn^{2+}
	pK_a	$pK_{a'}$	K_1	K_2	K_1	K_1	K_2	K_1	K_1	K_1
3-Hydroxyanthranilic acid *	10·09 ± 0·02	5·20 ± 0·01	—	—	7·7	5·1	3·6	4·4	4·3	3·4
2-Amino-4,5-dimethylphenol hydrochloride	10·40 ± 0·06	5·28 ± 0·04	9·9	—	—	5·9	4·8	5·3	4·9	3·6
2-Aminophenol hydrochloride	9·99 ± 0·02	4·86 ± 0·04	8·8	7·3	8·0	5·4	—	4·7	4·3	3·6

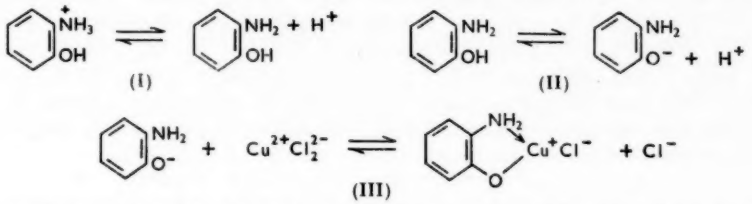
* Albert (personal communication) reports pK_a 5·21 ± 0·01 and 10·11 ± 0·03 for 3-hydroxyanthranilic acid at 20°, and values of 5·07 and 3·31 for the stability constants of the complex of this acid with Ni^{2+}.

at these low concentrations precipitation of the complexes began at values of $\bar{n}$ of 0·8 or above for 2-amino-4,5-dimethylphenol and 2-aminophenol and at 0·6 and above for 3-hydroxanthranilic acid. Values for K_2 are recorded where precipitation did not occur below $\bar{n} = 1·5$. The pK_a values for the aminophenols presumably refer to the equilibria (I) and (II). A third pK_a of about 2·5 for 3-hydroxyanthranilic acid could not be measured exactly because of difficulties due to insolubility, but it is presumably that of the acid–base equilibrium involving the carboxyl group. K_1 is the equilibrium constant of reactions such as (III). Except in the presence of cupric or ferrous ions, the titration curves of the

[1] Boyland and Watson, *Nature*, 1956, **177**, 837.
[2] Allen, Boyland, Dukes, Horning, and Watson, *Brit. J. Cancer*, 1957, **11**, 212.
[3] Albert, *Biochem. J.*, 1950, **47**, 531.
[4] *Idem, ibid.*, 1952, **50**, 690.

XUM

hydrochlorides of 2-aminophenol and 2-amino-4,5-dimethylphenol with the metallic ions followed closely the titration curves in their absence until one equivalent of alkali had been added. 3-Hydroxyanthranilic acid behaved in the same way: presumably one of the functional groups (possibly carboxyl) is not involved in chelate formation. With cupric and ferrous ions complex formation began with all aminophenols during the addition of



the first equivalent of alkali. Ferric ions chelate strongly with all three aminophenols but, because of the low solubility of the complexes, the stability constants could not be measured, and the titration curves in the presence of Mg^{2+} ions closely followed those obtained in the absence of metallic ions. The order of stability of the chelates of the various metals follows that described by Irving and Williams [5] except that the position of the ferrous chelates is anomalous and the values of K_1 are higher than expected. This may be due to oxidation of ferrous to ferric ions, although *o*-aminophenols might be expected to act as reducing agents.

Albert [3] has pointed out that the success of a chelating agent in competing for a particular metallic ion depends on K_a as well as on the stability constants. This is reflected in the value of $\bar{n}$ at a given pH, and in particular at the pH of the animal cell. As the values of K_a and K_1 of the three aminophenols do not differ widely among themselves, little differences in the values of $\bar{n}$ at, say, pH 7·5, for each aminophenol with a particular metallic ion would be expected. For example, 3-hydroxyanthranilic acid, 2-amino-4,5-dimethylphenol, and 2-aminophenol in the presence of Ni^{2+} ions have values for $\bar{n}$ of 0·45, 0·20, and 0·37 respectively at this pH.

Experimental.—Materials. 3-Hydroxyanthranilic acid was prepared by Spada and Gavioli's method [6] and purified as described by Hegedüs.[7] 2-Amino-4,5-dimethylphenol, prepared by the persulphate oxidation of 3,4,1-xylidine,[8] and 2-aminophenol were purified by sublimation and converted into the hydrochlorides by saturating solutions in ether with dry hydrogen chloride.

The metallic ions were added in the form of the following "AnalaR" salts: Fe^{2+}, Co^{2+}, Mn^{2+}, and Mg^{2+} as sulphates, Ni^{2+} and Co^{2+} as the nitrates, and Cu^{2+} as the chloride.

Titrations. 5×10^{-5} mole of the aminophenol and $2{\cdot}5 \times 10^{-5}$ mole of the metallic salt, in boiled-out distilled water (45 ml.), were titrated with 0·01N-potassium hydroxide (carbonate free), added in 0·5 ml. portions, the pH of the solution being measured after each addition of alkali on a Pye Universal pH meter with a lithium-glass electrode and a calomel electrode. The titration vessel was immersed in a bath at 20° ± 0·1°, and the contents were stirred by means of a stream of purified nitrogen. pK_a was measured in the same way in the absence of metallic ions.

I thank Professor Adrien Albert for a discussion and Professor E. Boyland for his interest. This work was supported by grants to this Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

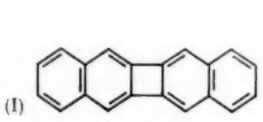
THE CHESTER BEATTY RESEARCH INSTITUTE,
THE INSTITUTE OF CANCER RESEARCH: ROYAL CANCER HOSPITAL,
LONDON, S.W.3. [*Received, May 26th*, 1959.]

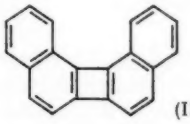
[5] Irving and Williams, *J.*, 1953, 3192.
[6] Spada and Gavioli, *Boll. scient. Fac. chim. ind. Bologna*, 1950, **8**, 101.
[7] Hegedüs, *Helv. Chim. Acta*, 1951, **34**, 611.
[8] Sims, *J.*, 1958, 44.

740. 2,3:6,7-*Dibenzodiphenylene.*

By R. F. Curtis.

Recently,[1] it was emphasised that 2,3:6,7-dibenzodiphenylene (I) shows unusual properties compared with 1,2:7,8-dibenzodiphenylene[2] (II). In particular, the melting point (372°) is very high and the compound is extraordinarily stable (sublimation unchanged at 350°). In contrast, 1,2:7,8-dibenzodiphenylene (II) (m. p. 137—139°) decomposes easily. Since it was impossible to determine the molecular weight of 2,3:6,7-dibenzodiphenylene these large differences might be attributed to a structure of higher molecular weight than that appropriate for (I), especially as only a low yield of 2,2′-dinaphthyl was obtained on reduction.


(I)


(II)

The mass spectrum of the compound has now been determined. This clearly shows a molecular weight of 252 ($C_{20}H_{12}$) and a breakdown pattern indicative of a diphenylene nucleus.

Thus the dibenzodiphenylenes (I) and (II) must contain major contributions from the structures shown, with cyclobutadienoid character predominant in (II) and notably absent from (I).

The mass spectrum was kindly determined by Imperial Chemical Industries Limited (Dyestuffs Division).

University College of Swansea,
Singleton Park, Swansea.

[*Received, May 28th,* 1959.]

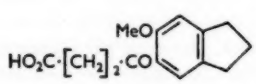
[1] Curtis and Viswanath, *J.*, 1959, 1670.
[2] Cava and Stucker, *J. Amer. Chem. Soc.*, 1955, **77**, 6022.

---

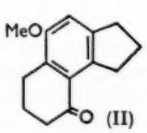
741. 6-*Hydroxy*-4,5-*benzindane.*

By David W. Mathieson and V. S. Gandhi.

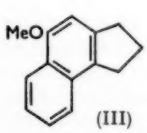
5-Methoxyindane has been condensed with succinic anhydride in presence of aluminium chloride to yield the propionic acid (I). Oxidation of this gave 5-methoxyindane-6-carboxylic acid whence demethylation yielded the known 5-hydroxyindane-6-carboxylic acid.[1] The position of attack on 5-methoxyindane under Friedel–Crafts conditions is thus demonstrated and is to be compared with production of 6-acetyl-5-hydroxyindane obtained on Fries rearrangement of 5-acetoxyindane.[2]



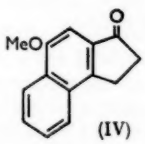
(I)



(II)



(III)



(IV)

Clemmensen reduction of the acid (I) followed by cyclisation with anhydrous hydrogen fluoride furnished the tetrahydrobenzindanone (II). A second reduction with amalgamated zinc followed by selenium dehydrogenation then yielded 6-methoxy-4,5-benzindane

[1] Prelog, Meltzer, and Jeger, *Helv. Chim. Acta*, 1947, **30**, 675.
[2] Wilson Baker, *J.*, 1937, 476.

(III), whose constitution was confirmed by comparison with a sample obtained on Clemmensen reduction of the known [3] 6-methoxy-1-oxo-4,5-benzindane (IV).

Demethylation of the 6-methoxy-compound (III) gave 6-hydroxy-4,5-benzindane. The m. p. of this phenol is in accord with that of a sample isolated by Kruber [4] from coal tar by sulphonation followed by potash fusion.

Experimental.—*γ-(5-Methoxy-6-indanyl)-γ-oxobutyric acid* (I). Aluminium chloride (27 g.) was added with stirring to 5-methoxyindane (15 g.) and succinic anhydride (12 g.) in ethylene dichloride (100 ml.) and the mixture kept overnight. Next morning it was decomposed with ice and dilute hydrochloric acid. Solvent was removed by steam distillation and the residual solid purified *via* its sodium salt. The *acid* crystallised from ethanol in needles, m. p. 181—182·5° (Found: C, 67·9; H, 6·6; OMe, 12·6. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5; OMe, 12·5%).

Oxidation by means of alkaline sodium hypochlorite afforded 5-methoxyindane-6-carboxylic acid, m. p. 106°. This was demethylated with hydrogen bromide in acetic acid to give 5-hydroxyindane-6-carboxylic acid, m. p. 195° (Prelog, Meltzer, and Jeger [1] give m. p. 195—196°).

γ-(5-Methoxy-6-indanyl)butyric acid. To amalgamated zinc wool (40 g.) and water (80 ml.) there was added in order, concentrated hydrochloric acid (120 ml.) and *γ*-(5-methoxy-6-indanyl)-*γ*-oxobutyric acid (20 g.) in toluene (120 ml.). The mixture was refluxed for 48 hr., additions of concentrated hydrochloric acid (5—10 ml.) being made every 12 hr. The dried toluene layer yielded a solid (17·8 g., 94%) which was recrystallised from light petroleum (b. p. 60—80°), forming stout needles, m. p. 82—83°, of the *acid* (Found: C, 72·2; H, 7·7. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%).

1′,2′,3′,4′-Tetrahydro-6-methoxy-4′-oxo-4,5-benzindane (II). *γ*-(5-Methoxy-6-indanyl)butyric acid (10 g.) was kept for 3 days in anhydrous hydrogen fluoride. Evaporation of the hydrogen fluoride gave a residue which was washed in ether with sodium carbonate solution to remove any unchanged acid. The ethereal solution yielded a neutral residue (8·8 g., 95%) which was recrystallised from ethanol, giving a felted mass of needles, m. p. 81·5° of the *benzindanone* (Found: C, 77·9; H, 7·5; MeO, 14·4. $C_{14}H_{16}O_2$ requires C, 77·7; H, 7·4; MeO, 14·3%); $\lambda_{max.}$ 227 mμ (ε 17,460), 258 mμ (ε 3808). The *semicarbazone* crystallised from ethyl alcohol in needles, m. p. 218—219° (Found: C, 65·5; H, 7·1; N, 15·3. $C_{15}H_{19}O_2N_3$ requires C, 65·9; H, 7·0; N, 15·4%). The 2 : 4-*dinitrophenylhydrazone* crystallised from xylene in crimson needles, m. p. 259—260° (Found: C, 60·8; H, 5·5; N, 14·2. $C_{20}H_{20}O_5N_4$ requires C, 60·6; H, 5·1; N, 14·1%).

1′,2′,3′,4′-Tetrahydro-6-methoxy-4,5-benzindane. To amalgamated zinc wool (10 g.) and water (20 ml.), were added concentrated hydrochloric acid (15 ml.) and 1′,2′,3′,4′-tetrahydro-6-methoxy-4′-oxo-4,5-benzindane (5 g.) in toluene (30 ml.). The mixture was refluxed for 48 hr., small additions of concentrated hydrochloric acid being made every 12 hr. After working up in the usual way there resulted a yellow oil (4·48 g., 96%), b. p. 110—120°/0·5 mm. This *benzindane* crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 68° (Found: C, 82·9; H, 8·9; OMe, 15·4. $C_{14}H_{18}O$ requires C, 83·1; H, 8·9; OMe, 15·3%); $\lambda_{max.}$ 284 mμ (ε 2650), 333—334 mμ (ε 413). The *picrate* crystallised from ethanol in orange-red needles, m. p. 96—98° (Found: C, 55·8; H, 4·9; N, 9·7. $C_{20}H_{21}O_8N_3$ requires C, 55·7; H, 4·9; N, 9·8%).

6-Methoxy-4,5-benzindane (III). (*a*) The tetrahydro-compound (3 g.) was heated to 200° for 4 hr. with an equal weight of 30% palladium–charcoal, a stream of carbon dioxide being passed through the flask. After cooling, the residue was extracted with ether. The pale yellow oil was purified by passing the derived picrate through alumina, and the low-melting solid obtained was crystallised from light petroleum (b. p. 40°) at −40°. Colourless needles, m. p. 39·5°, of the *benzindane* (III) resulted (Found: C, 84·7; H, 7·2; MeO, 15·2. $C_{14}H_{14}O$ requires C, 84·8; H, 7·1; MeO, 15·7%); $\lambda_{max.}$ 241 mμ (ε 35,330), 303 mμ (ε 5283). The *picrate* crystallised in dark red needles, m. p. 154—155°, from ethanol (Found: C, 56·2; H, 4·0; N, 9·8. $C_{20}H_{17}O_8N_3$ requires C, 56·2; H, 4·0; N, 9·8%). (*b*) A mixture of 6-methoxy-1-oxo-4,5-benzindane (5 g.) in toluene (30 ml.) and zinc amalgam (10 g.) in concentrated hydrochloric acid (30 ml.) and water (20 ml.) was heated under reflux for 48 hr. The ether-soluble portion of the product was a pale yellow oil, b. p. 140—150°/0·1 mm. (39%), which solidified on cooling and was purified by passing the picrate through alumina. Crystallisation from light petroleum

[3] Robinson and Martin, *J.*, 1943, 798.
[4] Kruber, *Ber.*, 1932, **65**, 1382.

(b. p. 40°) at −40° gave needles, m. p. 39° giving no depression on admixture with a sample obtained by method (*a*); $\lambda_{max.}$ 241 mμ (ε 37,360), 303 mμ (ε 5564). The picrate crystallised from ethanol in dark red needles, m. p. 150—151° giving no depression on admixture with a sample prepared as described under (*a*).

6-*Hydroxy*-4,5-*benzindane* (IV). 6-Methoxy-4,5-benzindane (850 mg.) was refluxed with 60% aqueous hydrobromic acid (4 ml.) and acetic acid (7 ml.) for 4 hr. Most of the solvent was removed *in vacuo*, and phenolic material removed by washing an ethereal solution of the residue with sodium hydroxide. The non-phenolic fraction (405 mg.) was again demethylated. The combined sodium hydroxide extracts yielded a solid (320 mg.) (40%), purified by passing an ethereal solution through a short column of charcoal. The sample was sublimed at 75—85°/0·1 mm., then crystallised from light petroleum (b. p. 60—80°) to give yellow needles, m. p. 120—121° (Kruber [4] records m. p. 122°) (Found: C, 84·7; H, 6·7. Calc. for $C_{13}H_{12}O$: C, 84·8; H, 6·5%).

THE SCHOOL OF PHARMACY, BRUNSWICK SQUARE,
LONDON, W.C.1.

[*Received, May 28th*, 1959.]

---

742. *Experiments Relating to Phthiocerol. Part IV.*[1] *Synthesis of 7-Methoxy-6-methylnonanoic Acid.*

By F. K. DRAYSON and N. POLGAR.

6-METHYL-7-OXONONANOIC ACID [1] was converted, by means of diazomethane, into its methyl ester which, on reduction with sodium borohydride in tetrahydrofuran, gave the hydroxy-ester. Methylation of the latter by repeated treatment with methyl iodide–silver oxide gave the methoxy-ester which on hydrolysis afforded the methoxy-acid. Comparison of the infrared spectra of the methoxy-ester and the methyl ester derived from the C_{11} oxidation product of phthiocerol showed close agreement. Moreover, Professor Ställberg-Stenhagen, of Göteborg, kindly subjected these methyl esters to gas chromatography, and found that, within the experimental error, they had the same gas-chromatographic retention time.

Experimental.—Petrol refers to light petroleum (b. p. 40—60°).

Methyl 7-*hydroxy*-6-*methylnonanoate*. 6-Methyl-7-oxononanoic acid [1] was converted, by means of diazomethane, into its *methyl* ester which distilled at 160—180° (bath)/17 mm., and had n_D^{23} 1·4368 (Found: C, 65·9; H, 10·0. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%). This ester (1·02 g.) in dry tetrahydrofuran (20 c.c.) was added dropwise to a solution of sodium borohydride (0·2 g.) in tetrahydrofuran (40 c.c.) during 6 hr., the mixture being stirred mechanically throughout. Most of the tetrahydrofuran was then removed by distillation, and the residue, after acidification with dilute sulphuric acid, was extracted with ether. Distillation of the dried ($MgSO_4$) extract gave *methyl* 7-*hydroxy*-6-*methylnonanoate* (0·95 g.), b. p. 160—190° (bath)/12 mm., n_D^{18} 1·4476 (Found: C, 65·2; H, 10·8. $C_{11}H_{22}O_3$ requires C, 65·3; H, 10·9%).

7-*Methoxy*-6-*methylnonanoic acid*. The hydroxy-ester (3·4 g.) was refluxed with methyl iodide (15 c.c.) and silver oxide (8 g.; prepared according to the directions of Busch *et al.*;[3] added in small portions) for 8 hr. The mixture was filtered while hot, and the silver salts were extracted repeatedly with boiling chloroform. The filtrate and washings were then evaporated. After three more methylations by the same procedure, the product was chromatographed in petrol on alumina (200 g.; Spence, type H, washed with 50% aqueous acetic acid, then dried at 175° for 36 hr.; activity II on Brockmann and Schodder's scale [4]) prepared in petrol. Elution with petrol afforded *methyl* 7-*methoxy*-6-*methylnonanoate* (1·6 g.) which distilled at 160—175° (bath)/20 mm., and had n_D^{23} 1·4339 (Found: C, 66·5; H, 11·3. $C_{12}H_{24}O_3$ requires C, 66·7; H, 11·1%). Further elution with petrol–benzene (1 : 1) yielded unchanged methyl 7-hydroxy-6-methylnonanoate.

The methoxy-ester was hydrolysed by refluxing 5% aqueous-ethanolic (1 : 1) potassium

[1] Part III, Drayson, Lewis, and Polgar, *J.*, 1958, 430.
[2] Hall, Lewis, and Polgar, *J.*, 1955, 3971.
[3] Busch, Clark, Genung, Schroeder, and Evans, *J. Org. Chem.*, 1936, **1**, 1.
[4] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.

XUM

hydroxide for 1 hr. Dilution with water, followed by acidification with hydrochloric acid and ether-extraction, afforded *7-methoxy-6-methylnonanoic acid*, b. p. 180—200° (bath)/18 mm., n_D^{20} 1·4458 (Found: C, 65·4; H, 11·1. $C_{11}H_{22}O_3$ requires C, 65·3; H, 11·0%). The *S-benzylthiuronium salt* crystallised from 50% aqueous ethanol as plates, m. p. 141—143° (Found: C, 62·2; H, 8·4; S, 8·4. $C_{19}H_{32}O_3N_2S$ requires C, 62·0; H, 8·7; S, 8·7%). Hall *et al.*[2] give m. p. 137—139° for the *S*-benzylthiuronium salt of the stereoisomer arising on oxidation of phthiocerol.

We thank the Department of Scientific and Industrial Research for a Maintenance Award (to F. K. D.).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, May 29th,* 1959.]

743. *Polyfluoroarenes. Part II.*[1] *The Ionisation Constant of Pentafluorophenol.*

By J. M. BIRCHALL and R. N. HASZELDINE.

THE replacement of hydrogen by fluorine in an alcohol causes a marked increase in ionisation constant, *e.g.*, $CH_3{\cdot}CH_2{\cdot}OH$, $K_a = 3 \times 10^{-16}$ (in water); $CF_3{\cdot}CH_2{\cdot}OH$, $K_a = 4{\cdot}8 \times 10^{-12}$ (in 50% aqueous ethanol).[2,3] The synthesis and properties of pentafluorophenol [1] suggest that the perfluoroarene ring exhibits distinct conjugation of the double bonds, in contrast to hexafluorobuta-1,3-diene.

The ionisation constant of pentafluorophenol, now determined as $K_a = 3{\cdot}0 \times 10^{-6}$ at 25°, is distinctly greater than that for phenol ($K_a = 1{\cdot}3 \times 10^{-10}$) [4] or the fluoro-alcohol $(C_3F_7)_2CH{\cdot}OH$ ($K_a = 30 \times 10^{-12}$),[3] and approaches that of benzoic acid, thus indicating the effect of conjugation in the ring. It also reveals the extent to which back-co-ordination with electron-release from fluorine, *e.g.*,

offsets the inductive effect of the aryl fluorine, since pentachlorophenol [5] is more acidic, with $K_a = 5{\cdot}5 \times 10^{-6}$. Fluoro-alcohols are more acidic than the corresponding chloro-alcohols [$CF_3{\cdot}CH_2{\cdot}OH$, $K_a = 4{\cdot}8 \times 10^{-12}$; $CCl_3{\cdot}CH_2{\cdot}OH$, $K_a = 1{\cdot}6 \times 10^{-12}$; $(CF_3)_2CH{\cdot}OH$, $K_a = 50 \times 10^{-12}$; $(CCl_3)_2CH{\cdot}OH$, $K_a = 7 \times 10^{-12}$].[3]

Electron-release by fluorine has been noted earlier in monofluoro-aromatic compounds [K_a for *p*-fluorophenol,[6] $1{\cdot}1 \times 10^{-10}$; *p*-chlorophenol,[7] $4{\cdot}2 \times 10^{-10}$; *p*-fluorobenzoic acid,[8] $7{\cdot}2 \times 10^{-5}$; *p*-chlorobenzoic acid,[9] $10{\cdot}3 \times 10^{-5}$; benzoic acid,[10] $6{\cdot}3 \times 10^{-5}$], but it is now clear that polyfluoroarenes show the same effect.

Experimental.—The ionisation constant for pentafluorophenol [1] was determined by measurement of the pH of an aqueous solution, titrated against aqueous sodium hydroxide, at the half-neutralisation point; [6] application of the Henderson equation gives pH = pK_a. Solutions were 0·01N in carbonate-free distilled water and 50 ml. aliquot portions were titrated; pH measurements (Model 23A Electronic Instruments Ltd. pH meter with glass electrode) were reproducible to ±0·01 unit. Repeated determinations gave pK_a = 5·53, whence $K_a = 2{\cdot}95 \times 10^{-6}$.

MANCHESTER COLLEGE OF SCIENCE AND TECHNOLOGY. [*Received, June 1st,* 1959.]

[1] Part I, *J.*, 1959, 13.
[2] Danner and Hildebrand, *J. Amer. Chem. Soc.*, 1922, **44**, 2824.
[3] Haszeldine, *J.*, 1953, 1757, and unpublished results.
[4] Walker and Cormack, *J.*, 1900, **77**, 18.
[5] Tiessens, *Rec. Trav. chim.*, 1931, **50**, 112.
[6] Bennett, Brooks, and Glasstone, *J.*, 1935, 1821.
[7] Judson and Kilpatrick, *J. Amer. Chem. Soc.*, 1949, **71**, 3110.
[8] Dippy, Williams, and Lewis, *J.*, 1935, 343.
[9] Briegleb and Bieber, *Z. Electrochem.*, 1951, **55**, 250.
[10] Dippy and Williams, *J.*, 1934, 1888.

744. *Measurement of the Conductance of Electrolytes.*

By W. S. METCALF.

THE resistance of an electrolyte is usually measured by using some modification of the Wheatstone bridge such as that of Fig. 1. The resistance R_2 and capacitance C_2 of the test cell are balanced by the variable resistance R_1 and a variable capacitance C_1 in *parallel* with it. However the capacitance of the test cell resides mainly on the surface of the electrodes as a layer of undischarged ions and is in *series* with the resistance R_2 of the electrolyte.[1] The reactance of the electrolyte cell is thus of the form C_2'–R_2–C_2''.

The conditions of balance require

$$R_1 = R_2\left(1 + \frac{1}{\omega^2 R_2^2 C_2^2}\right); \quad C_1 = \frac{C_2}{(1 + \omega^2 R_2^2 C_2^2)}$$

where $1/C_2 = 1/C_2' + 1/C_2''$. Both R_1 and C_1 depend on both R_2 and C_2 and on the frequency. As R_2 changes, as is the case when the rate of a reaction is followed by a change of conductance, C_1 must be continually adjusted to maintain the bridge in balance. At low frequencies (50 cycles per sec.), C_1 is inconveniently large.

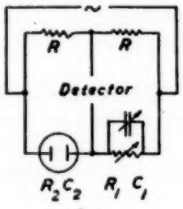


Fig. 1

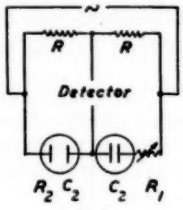


Fig. 2

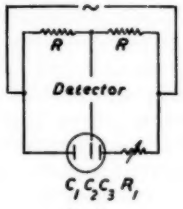


Fig. 3

If C_1 is put in series with R_1 its value at balance should be independent of R_2 and of frequency. This arrangement is simpler to manipulate, and more suited to automatic recording and control equipment.

The capacity of the cell can be balanced by that of a similar cell of the same electrolyte with electrodes of the same size but closer together, as in Fig. 2. At balance R_1 is proportional to the specific conductance of the electrolyte.

Experimentally, it is simpler to adopt the arrangement of Fig. 3. Three similar electrodes,[2] of which one pair are more closely spaced than the others, are sealed into the same glass cell.

The specific resistance of the electrolyte is proportional to R_1 at balance, and the constant of proportionality (" cell constant ") is measured in the conventional way.

If C_1, C_2, C_3 are the surface capacities of the electrodes and R_{12}, R_{23}, R_{31} are the inter-electrode resistances, the conditions for balance are

$$R_1 = \frac{R_{31}(R_{12} - R_{23})}{R_{12} + R_{23} + R_{31}}; \quad C_1 = C_3$$

A highly sensitive yet simple instrument for use at 50 cycles per sec. can be made with short bright platinum wire electrodes. If the electrodes are platinised the duration of the plating process can be controlled to secure the precise equivalence of C_1 and C_3.

This arrangement of three electrodes has proved suitable in equipment (made and tested by the Industrial Development Division of this University) for the automatic recording and control of the conductance of an alkaline solution for cleaning milk bottles. The capacity balance changes very little as the electrodes become contaminated with grease, and no separate automatic capacity balance is required.

UNIVERSITY OF CANTERBURY, CHRISTCHURCH, NEW ZEALAND. [*Received, June 18th*, 1959.]

[1] Feates, Ives, and Pryor, *J. Electrochem. Soc.*, 1956, **103**, 580.
[2] Shedlovsky, *J. Amer. Chem. Soc.*, 1930, **52**, 1806.